January 1982 Vol. 66 No. 1

CUK-[illegible]-9-P25378

British Journal of
Ophthalmology

8

BRITISH MEDICAL ASSOCIATION TAVISTOCK SQUARE LONDON WC1H 9JR

P 25,378

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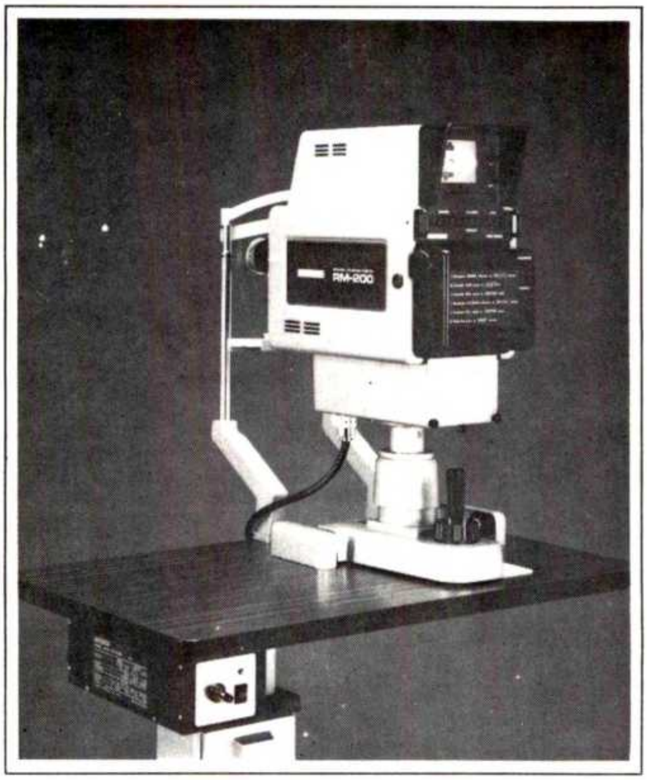

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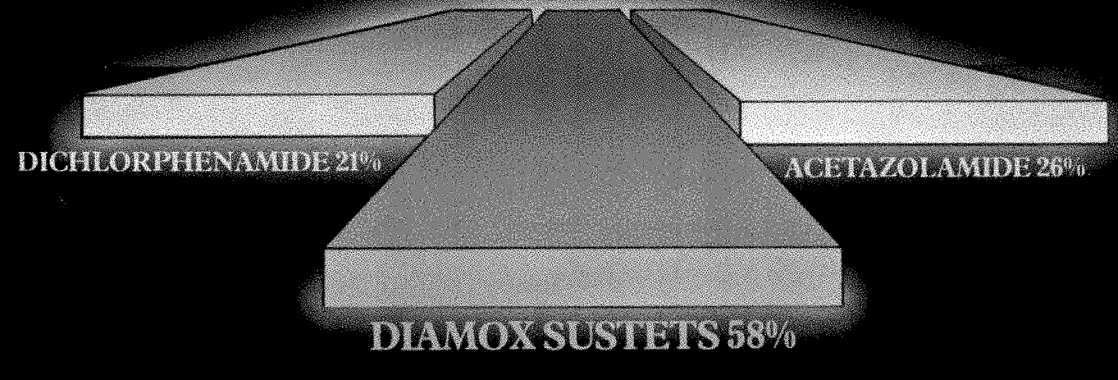

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British Journal of Ophthalmology, 1982, 66, 1-16

Retinal pigment epithelial detachments in the elderly: a controlled trial of argon laser photocoagulation

THE MOORFIELDS MACULAR STUDY GROUP*

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SUMMARY A prospective randomised trial of argon laser photocoagulation of retinal pigment epithelial detachments in the elderly is presented. The results based on 18 months' follow-up show that, in terms of visual acuity, photocoagulation is not beneficial as carried out in this study. The morphological outcome of the treated and untreated eyes is discussed. Stricter entry criteria would not have affected the conclusions. Tearing of the pigment epithelium occurred earlier in the treated than in the untreated eyes.

1. VISUAL OUTCOME

Retinal pigment epithelial detachments occurring in the presence of diffuse, age-related, Bruch's membrane changes and drusen, but without detectable subretinal neovascularisation, form part of the spectrum of senile macular degeneration.[1] They present a typical appearance of discrete, round or oval, dome shaped lesions which, on fluorescein angiography, fill early and evenly with dye and continue to fluoresce after the background has faded.[2 3] Pigment epithelial detachments may progress to vascular disciform lesions, and it has been thought that this development is consistently associated with deterioration of the visual acuity.[4 5] It is recognised that the presence of subretinal new vessels cannot be excluded by clinical criteria alone.[6] However, the behaviour of apparently avascular lesions differs significantly from those with identifiable subretinal neovascularisation, and therefore their separate consideration is justified.

Treatment of pigment epithelial detachments by photocoagulation was first reported in 1968.[7] In the early reports either xenon arc photocoagulation was applied in a horseshoe shaped pattern[8] or, alternatively, pulsed ruby laser burns were scattered over the lesion.[9] Later reports described argon laser grid photocoagulation of the detachment avoiding the foveola.[10-12]

In one of the earlier studies 47 out of 53 detachments flattened following treatment and remained flat during the follow-up period without loss of visual acuity.[13] More recent evidence suggested that patients under the age of 56 had a good visual prognosis without treatment.[14 15] By contrast older patients and those with detachments larger than one disc diameter appeared to have a much higher risk of vascular complications and visual loss.[15] Although the initial photocoagulation studies had implied a possible benefit from treatment, a more recent study has suggested that this may not be the case.[16] Furthermore, a significant number of young patients who have a good visual prognosis were included in the earlier studies.[11 14 15] No controlled trial of treatment has yet been reported.

The purpose of this paper is to present the results of a prospective, randomised, controlled trial of argon laser photocoagulation in the treatment of pigment epithelial detachments in the elderly. The study has been carried out over a 4-year period, and the conclusions are based on a follow-up period of 18 months.

Material and methods

STRUCTURE OF THE STUDY

The purpose of the study was to determine whether argon laser photocoagulation altered the visual prognosis of pigment epithelial detachments in the

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elderly and whether the age of the patient, the location of the detachment, or the presenting visual acuity influenced the final outcome.

Entry criteria. Patients were considered suitable for entry according to the following criteria: (1) evidence of a pigment epithelial detachment extending to within 1500 μm of the centre of the fovea and which could underlie the foveola; (2) absence of detectable subretinal new vessels on angiography; (3) age limits of 50 to 80 years; (4) presence of drusen in both eyes; (5) consensus of opinion from the medical workers concerning the patient's suitability for the trial.

Exclusion criteria. Patients were excluded for the following reasons: (1) subretinal exudates and/or haemorrhages which implied the presence of subretinal vessels and which precluded adequate view of subretinal structures; (2) diseases which precluded adequate fundus examination and laser photocoagulation; (3) other disease associated with visual loss; (4) myopia of greater than 3 dioptres; (5) previous photocoagulation in the eye under consideration; (6) inability or unwillingness to give informed consent.

PATIENT MANAGEMENT

Initial visit. Clinical assessment, colour photography and fluorescein angiography were carried out on this occasion. Guttae phenylephrine 10%, and cyclopentolate 1% were used for mydriasis prior to fundus examination and photography. Fundi were examined by indirect ophthalmoscopy and biomicroscopy with the Zeiss (Oberkochen) slit-lamp with a Hruby lens attachment. Stereoscopic colour photographs were taken with the Zeiss Retinophot fundus camera using Ektachrome film. Stereo fluorescein angiography was carried out with the Zeiss (Oberkochen) fundus camera, Ilford FP4 film, and Spectrotec filters following an intravenous injection of 5 ml 20% fluorescein sodium *BP*. If on the basis of the clinical findings it was believed that the criteria for entry were satisfied, with no cause for exclusion, the patient was asked to return on the next available day for further evaluation.

Entry study visit. The entry visit was carried out within 4 days of the initial angiogram. The photographs were examined, and, if the entry criteria were satisfied, the nature of the study was explained to the patient, who was invited to enter the treatment trial. Informed consent was obtained prior to entry. Evaluation of the visual acuity and visual field assessment were carried out prior to stratification and randomisation.

Visual function before mydriasis was assessed by an ophthalmic optician at the entry study visit. The best corrected Snellen distance acuity and near vision acuity with a +4 dioptre reading addition were measured with the Faculty of Ophthalmologists reading test type for near vision. When the acuity was worse than N5 with a +4 dioptre addition, the best reading acuity with low vision aids was recorded; the type and power of the aids needed was noted. The data were converted to a numerical value for analysis (Table 1).

Table 1 *Visual acuity data conversion*

6/5 = 1	N5 = 1
6/6 = 2	N6 = 2
6/9 = 3	N8 = 3
6/12 = 4	N10 = 4
6/18 = 5	N12 = 5
6/24 = 6	N14 = 6
6/36 = 7	N18 = 7
5–6/60 = 8	N24 = 8
4–3/60 = 9	N36 = 9
2–1/60 = 10	N48 = 10
Less than 1/60 = 11	Less than N48 = 11

Visual fields were assessed with a Friedmann Mk 1 field analyser. The macular threshold level was identified for the affected eye and static field recordings started 0·2 log units brighter than threshold. Errors were plotted on the standard chart and a note made of the error score in the central 9 and 33 points (8 or 32 plus fixation). The number of absolute defects and the error score for both the central 9 and 33 points were used for analysis.

The patients were then stratified according to age (50–60, 61–80), visual acuity (6/24 or better, or worse than 6/24) and distance of the nearest edge of the detachment from the foveola as measured by a grid[17] (less than 200 or 200–1500 μm). Random numbers arranged in cells of 4 within each stratum were used to allocate patients for treatment or observation, so that 2 patients from each cell received photocoagulation.

Treatment. At the end of the entry visit patients allocated to treatment were photocoagulated. Treatment was performed by the member of the medical team entering the patient into the trial, using the Coherent Radiation series 800 or 900 argon laser photocoagulator with a Zeiss delivery system. Topical anaesthesia and a Goldmann contact lens were used. Focal burns (usually 200 μm) were scattered in a grid pattern over the surface of the pigment epithelial detachment leaving a gap of approximately 200 μm between each. Care was taken to avoid the foveola and the major vessels. The power setting and duration of the burns (usually 0·2 s) were adjusted to produce definite whitening at the level of the pigment epithelium (Figs. 1a,b). Colour photographs were obtained immediately after the treatment, providing a permanent record.

Treatment visits. Subsequent visits were at 2-weekly intervals until no further photocoagulation

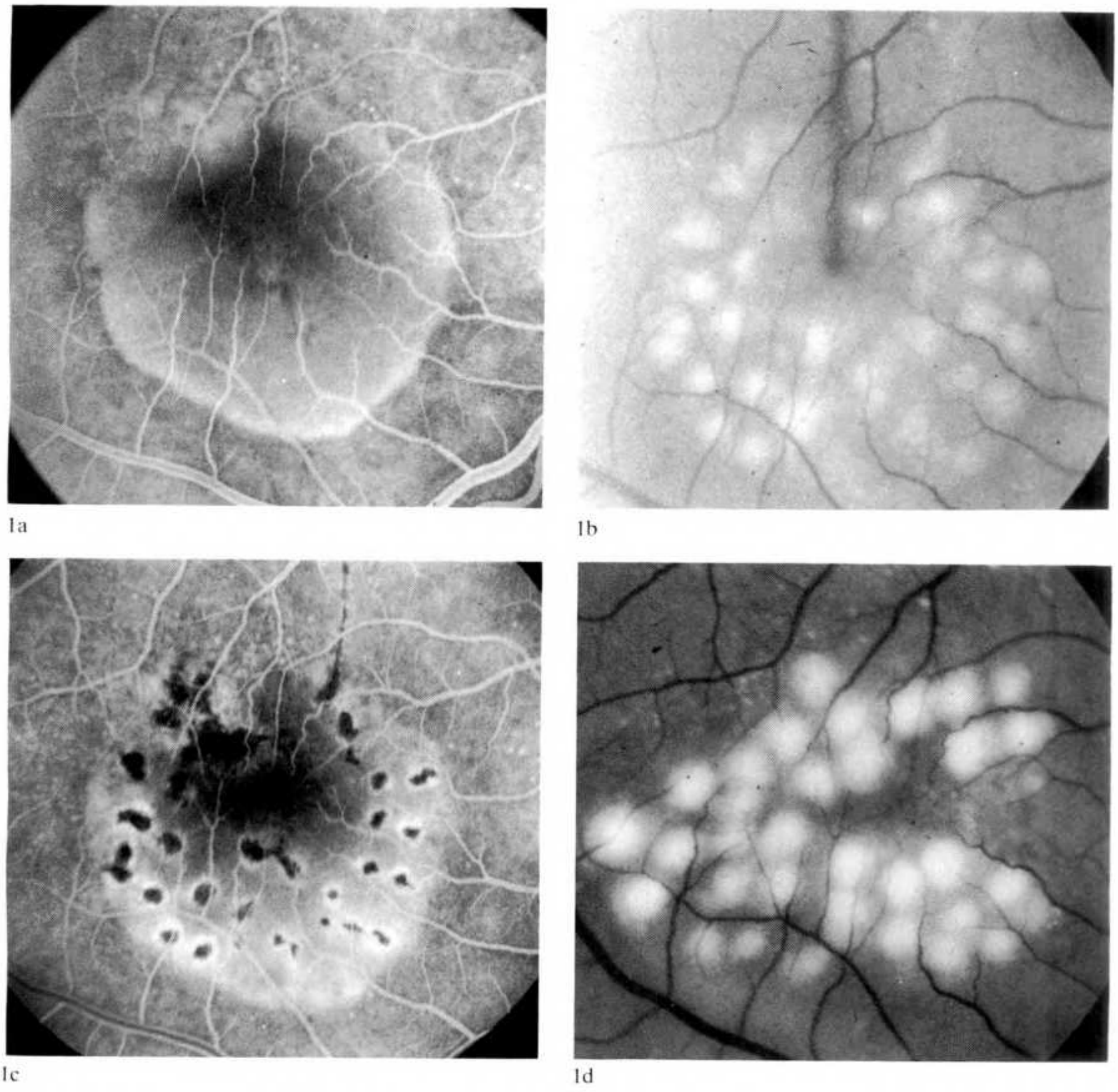


Fig. 1 *Treated pigment epithelial detachment:* (a) *before treatment;* (b) *immediately after treatment showing focal whitening over the surface of the detachment;* (c) *persistence of the detachment 2 weeks later despite photocoagulation;* (d) *retreatment of the persistent detachment.*

was indicated. Photocoagulation was repeated if there was persistence of the pigment epithelial detachment or neovascular tissue was detected under the retina (Figs. 1c,d). Neovascular lesions were treated with heavy confluent photocoagulation. The presence of subfoveolar neovascular tissue was a contraindication to additional treatment. Clinical examination, fluorescein angiography, and colour photography were repeated at each of these visits.

Study visits. Study visits were at 3-monthly intervals in the first year and 6-monthly thereafter for both treated and untreated patients (3, 6, 9, 12, 18 months). Visual acuity and field assessments were carried out by an ophthalmic optician on each visit, followed by further clinical examination, fundus photography, and fluorescein angiography.

Records were kept of intended visits, so that a missed appointment for a treatment or a study visit was rapidly recognised. In this event the patient was recalled so as to obtain data as close as possible to the date of the planned visit and not later than 6 weeks after a study visit. The patient was instructed to return for further assessment if at any time after the initial treatment visits there was a deterioration of vision. The photographs of treated patients were reviewed at 2-weekly intervals as part of an audit of management. If recurrent disease was identified, the patient was recalled for reassessment.

The visual acuity data, together with the field error scores, were analysed statistically at 3-monthly intervals. Both the optician and the statistician were masked from the treatment status of the patient. The statistical findings were passed to the Data Monitoring Committee at regular intervals.

STATISTICAL METHODS

Qualitative analysis

The purpose of this analysis was to compare the changes of visual acuity within the 2 management groups, a movement of 1 line (1 unit) and 2 lines (2 units) being used as a definition of change. The visual acuity at each study visit was compared with the initial findings and categorised as improved, unchanged, or worse.

To compare the proportion of eyes with deterioration in vision in the 2 groups standard deviate z was computed.[18] Significance values can be obtained from z values with tables of the normal distribution. As the accumulating data were subjected to analysis every 3 months, caution was exercised when deciding upon the p value which was to be considered 'significant'. At the start of the trial an overall p value for this qualitative analysis of 0·05 was designated as indicating a significant difference between the 2 groups; because the data could have been analysed a maximum of 10 times, the p value required for 'significance' at any one analysis, was taken to be 0·01[19] (p. 420), giving an approximate overall value of 0·05 for the qualitative analysis. The proportion of patients with improved vision was analysed similarly.

As stratification had been used in allocating the patients, Cochran's test statistic[20] was also calculated. However, as the randomisation procedure ensured that approximately equal numbers of patients from each stratum were allocated to the 2 groups, the z value is given in the tables. A chi-squared test for trend[19] (p. 363) was also performed on the proportions that showed improvement, no change, and deterioration in the 2 groups.

Quantitative analysis

The size of visual change between the 2 groups was compared, movement of one line of the Snellen chart being used as a unit of movement. Although the data were discrete, the normal approximation was used, and this enabled the data to be analysed by *t* tests. As in the qualitative analysis the overall significance level was set at 0·05 and the level of each analysis at 0·01.

Visual field analysis

To test for any difference in field scores a separate *t* test was used on the mean field changes for each of the 4 field readings.

End-point analysis

If the main objective of any treatment is to prevent deterioration of the patient's central vision below a certain level, regardless of initial visual acuity, it is useful to consider the patient's visual acuity at the time of entry into the study and at the time of examination.

For each patient at each visit it was recorded whether visual acuity had been worse than the end-point at least once, twice, or 3 times consecutively.

A separate analysis was undertaken with an end-point of 6/24, 6/36, and 6/60. The proportion of patients having a particular event recorded in the 2 management groups was compared by means of the z value; an approximate overall p value of 0·01 was considered significant. As stratification was used, Cochran's test statistic was evaluated.[20] However, the z value and Cochran's statistic were similar in all analyses, and only the z value is given in the tables.

Results of the main study

SIZE OF STUDY AND FOLLOW-UP

Of the 22 patients in the treatment group 18 attended every follow-up visit for 18 months. One patient died between the 3 and 6 months' visits. Visits were missed at 6 and 9 months by one patient, at 6 months by another, and the last was not seen between 6 months and 2 years (Table 2).

Of the 27 control patients complete follow-up information was recorded for 23. One left the study after the initial visit to be treated elsewhere. One

Table 2 *Number of patients who had completed the indicated visit by 30 September 1980*

Visit	*Group*	
	Treated	*Untreated*
Initial	22	27
3 months	22	26
6 months	19	25
9 months	19	24
12 months	20	25
18 months	20	24

Table 3 *The change in visual acuity from the initial visit to the visit indicated*

A. Taking a move of one or more lines as a change

Visit months	*Group*								
	Treated			*Untreated*					
	Improved	*Same*	*Worse*	*Improved*	*Same*	*Worse*	*Zi*	*Zw*	$\chi^2 t$
3	1	8	13	4	17	5	−1·25	2·82*	7·55*
6	1	4	14	5	10	10	−1·46	2·24	4·92
9	1	5	13	4	10	10	−1·19	1·75	3·24
12	1	5	14	4	10	11	−1·20	1·75	3·24
18	1	4	15	4	6	14	−1·24	1·17	1·84

B. Taking a move of two or more lines as a change

Visit months	*Improved*	*Same*	*Worse*	*Improved*	*Same*	*Worse*	*Zi*	*Zw*	$\chi^2 t$
3	0	14	8	1	23	2	−0·97	2·39	6·50
6	0	11	8	1	22	2	−0·97	2·59*	7·53*
9	0	11	8	0	20	4		1·82	
12	0	9	11	0	19	6		2·11	
18	0	6	14	0	14	10		1·89	

Zi: the Z value comparing the proportion of patients with improved acuity in each group.
Zw: the corresponding value for deterioration of visual acuity.
χ^2t: the value of the χ^2 variate testing for trend.
*: $p<0·01$.

patient died after having been seen at 3 months. Of the remaining 2 patients, one was lost to the study after 12 months and one missed the 9-month visit.

It was initially envisaged that, given the results of the preliminary study, approximately 150 patients would be required for the trial to be statistically valid. However, the study was designed to permit early termination if the Data Monitoring Committee thought that there was sufficient evidence to stop recruitment in the light of the results of any of the interim analyses. After approximately 40 patients had been followed up for at least one year, recruitment to the trial was stopped.

QUALITATIVE ANALYSIS

The percentage of patients showing any improvement in visual acuity was low in both groups, even when a move of one unit was taken as the criterion for change (Table 3A). The percentage that improved by at least one unit in the untreated group might have been greater than that in the treated group, but a much larger study would be required to show this. However, it is unlikely that treatment is beneficial if qualitative improvement in visual acuity is the basis for comparison.

There was strong evidence to suggest that the proportion of patients whose visual acuity deteriorated after photocoagulation was greater than that in the untreated group. This was particularly marked 3 months after treatment when a move of one or more units was taken as a change. At this time 61% of the treated patients had deteriorated, compared with 16% of the untreated ($z=2·82$, $p<0·01$). Between 9 and 18 months the percentage who deteriorated in the treated group remained fairly stable, whereas in the untreated group the percentage was steadily rising, but still some way from reaching the level in the treated group.

With a movement of 2 lines on the Snellen chart being taken as the criterion for change both groups showed steady increase in the proportion of patients who had deteriorated; the treated group consistently had the higher percentage (Table 3B). Although none of the z values obtained was significant at the 1% level, with more patients it is likely that the appropriate level of significance would have been obtained at each visit.

QUANTITATIVE ANALYSIS

The results (Table 4) showed that treated patients were prone to a large deterioration in visual acuity shortly after treatment, and it was this analysis that was the primary reason for termination of recruitment. The *t* values at the 3, 6, and 9 months visits were calculated with separate variance estimates, since the variance of the change in visual acuity was far greater in the treated group ($p<0·001$) at each of the first 3 visits. However, large and sudden deteriorations can also take place in the untreated group, albeit at a later stage. This is reflected in the standard deviation of the change in visual acuity in the untreated group, which increased at each visit.

Table 4 *Number of lines moved on Snellen chart since initial visit*

Number of lines	*Visit*									
	3 months		*6 months*		*9 months*		*12 months*		*18 months*	
	T	*U*	*T*	*U*	*T*	*U*	*T*	*U*	*T*	*U*
Worse −8	1	0	2	0	2	0	1	0	0	1
−7	0	0	1	0	0	0	1	1	2	1
−6	1	0	1	0	2	0	2	0	2	1
−5	3	0	3	0	3	0	4	0	4	1
−4	0	0	0	0	0	1	0	1	0	0
−3	2	0	1	0	0	1	2	2	2	2
−2	1	2	0	2	1	3	1	2	4	4
−1	5	3	6	8	5	6	3	5	1	4
Same 0	8	17	4	10	5	10	5	10	4	6
Better 1	1	3	1	4	1	4	1	4	1	4
2	0	1	0	1	0	0	0	0	0	0
Mean	−1·86	−0·77	−2·73	−0·24	−2·63	−0·50	−2·85	−0·88	−3·0	−1·67
SD	2·46	0·85	3·00	0·97	2·97	1·18	2·80	1·83	2·58	2·55
t	−3·25*		−3·50*		−2·95*		−2·84		−1·72	
P	0·003		0·002		0·007		0·007		0·09	

T=treated group; U=untreated group; SD=standard deviation; *indicates that separate variance estimates were used to calculate *t*.

END-POINT ANALYSIS

As would be expected from the results of the qualitative and quantitative analyses, the proportion of patients reaching a specified end-point was greater in the treated group for all 3 end-points used at each visit after entry into the trial (Table 5). The difference reached a maximum at 6 months (2·59 for 6/36) and decreased steadily thereafter. All treated patients who reached the lower end-points—i.e., 6/36 and 6/60—had done so by 6 months, but in the untreated group the number reaching these end-points appeared to be increasing at each subsequent visit.

VISUAL FIELDS

The field scores in both groups of patients generally showed a steady deterioration during the first 18 months (Table 6). It was only in the first 6 months after entry into the trial that any differences between the 2 groups were large enough to be detected and then only for the 'missed central' scores ($p<0·01$ at both 3 and 6 months). Other differences might have existed, but the standard deviations of the change in field scores were such that a far larger trial would have been required to detect them.

Baseline Variables

The variables used for the purposes of stratification were distance from the foveola, age, and visual acuity. However, except for age, any comparison of subgroups was either impossible or redundant, since the results would be merely a reflection of the trial results as a whole.

All analyses previously mentioned were carried out separately for patients aged 60 or less at the time of entry and for patients aged over 60. The results did not indicate that there was any interaction between age and the effect of treatment or that age influenced the outcome, although small differences could not have been discounted.

Table 5 *Number and percentage of patients who had visual acuity less than the specified end-point at one or more visits and had completed the visit indicated or a subsequent visit*

A=6/36

Visit	*Group*				*Z*
	Treated		*Untreated*		
	Number	*%*	*Number*	*%*	
Initial	0	0	1	3·7	−0·96
3 months	6	27·3	2	7·7	1·78
6 months	8	42·1	2	8·0	2·59*
9 months	8	42·1	3	12·5	2·16
12 months	9	45·0	4	16·0	2·10
18 months	9	45·0	6	25·0	1·39

B=6/60

Visit	*Treated Number*	*%*	*Untreated Number*	*%*	*Z*
Initial	0	0	0	0	0
3 months	3	13·6	0	0	1·87
6 months	5	26·3	0	0	2·56
9 months	5	26·3	0	0	2·54
12 months	5	25·0	2	8·0	1·53
18 months	5	25·0	4	16·7	0·68

*$p<0·01$.

Table 6 *The change in field scores from the initial visit to the visit indicated*

Visit	*Group*				*t*	*p*
	Treated		*Untreated*			
	Mean	*SD*	*Mean*	*SD*		
A: Error total						
3 months	−18·2	63·4	−18·1	39·5	−0·01	0·99
6 months	−19·2	101·9	−23·9	83·9	0·16	0·87
9 months	−10·6	82·6	−43·2	96·7	1·13	0·27
12 months	−26·4	81·6	−52·7	98·2	0·90	0·37
18 months	−27·8	88·0	−40·4	91·3	0·44	0·66
B: Error central						
3 months	−20·6	27·3	−5·3	18·7	−2·22	0·03
6 months	−18·7	33·4	−9·7	30·5	−0·90	0·37
9 months	−16·8	29·4	−23·5	36·7	0·62	0·54
12 months	−22·0	28·5	−25·7	40·2	0·34	0·74
18 months	−24·5	26·7	−27·9	37·2	0·33	0·75
C: Missed total						
3 months	2·90	7·0	1·00	5·7	1·01	0·32
6 months	1·56	6·4	1·87	5·9	−0·16	0·87
9 months	0·72	5·4	2·82	7·6	−0·99	0·33
12 months	1·00	5·4	3·74	6·6	−1·45	0·15
18 months	2·58	5·5	4·95	6·5	−1·24	0·22
D: Missed central						
3 months	2·14	2·6	0·38	1·3	2·85	0·008
6 months	2·61	3·0	0·26	1·1	3·18	0·009
9 months	2·50	2·7	1·32	2·8	1·33	0·19
12 months	2·89	2·7	1·65	3·3	1·32	0·19
18 months	2·84	2·3	2·24	3·3	0·67	0·51

Discussion

The study was carried out at a single centre, which ensured good control of both the patient visits and the standard of assessment and treatment. A limited number of workers was involved, and close co-operation was readily achieved. The decision about admissibility of a particular patient was made at the time of the second visit with all the medical workers present agreeing to entry. The records of the treated patients were audited following each visit, which ensured a uniformity of management.

The recruitment rate was lower than had been anticipated, but those patients who were admitted co-operated well. There was a low failure rate, and data were collected at 18 months on all but 5 patients, 2 of whom had died during the course of the study.

After 49 patients had been entered into the trial it was evident that the change in visual acuity was significantly worse in the treated group, and the Data Monitoring Committee decided that recruitment should be discontinued. A large deterioration of vision occurred in a significant number of treated patients soon after photocoagulation; such a deterioration was not seen in patients in the observation group during the early period after entry into the trial. It is clearly shown that with photocoagulation, as used in this study, there is no short-term visual benefit to elderly patients with pigment epithelial detachments.

The trial also shows that in the observation group rapid loss of vision could occur at any time. This contrasted with the treated patients, in whom additional visual loss was unusual after the initial period. However, at the 18-month visit the convergence between the 2 groups was insufficient to cancel out the early differences, and there is a little evidence to date to imply that a cross-over might occur later.

In designing the study it was thought that stratification into the groups described might show that a particular group would benefit from photocoagulation whereas another might not. The majority of patients were in the group with better acuity and had detachments within 200 μm of fixation. These patients were almost evenly divided between those from 50–60 years old and those over 60; comparison of these subgroups showed that photocoagulation conferred no benefit to either. Pigment epithelial detachments outside the central 200 μm or those associated with poor visual acuity rarely presented for assessment, which is consistent with clinical experience. There is no indication that any subgroup benefited from photocoagulation, although in some groups the numbers were so small that only gross differences would have been revealed.

2. MORPHOLOGICAL OUTCOME

Introduction

It has been assumed that the major threat to vision in patients with detachment of the retinal pigment epithelium is invasion of the subpigment epithelial space by blood vessels derived from the choroid,[5, 14–16] and that this complication can be prevented if photocoagulation causes flattening of the detachment.[11]

The evolution of the lesions is correlated with the visual outcome in patients admitted to this trial.

Results

TREATED PATIENTS

Of 21 patients at the end of the review period the pigment epithelium and retina were flattened in 13, there was persistence of the detachment in 2, and a vascular disciform lesion in 4 (Fig. 2). In the remaining 2 patients a tear in the pigment epithelium occurred immediately after photocoagulation, causing poor acuity, and was followed by submacular fibrosis (Fig. 3). In both cases incorrect identification of the lesion led to further treatment.

Of those patients with flattening of the retinal pigment epithelium 4 had one, 8 had 2, and 1 had 3 sessions of photocoagulation. The flattening occurred within 2 weeks of the final treatment. In none did the visual acuity improve, in 7 the acuity remained within one line of the pretreatment level, and in the remainder a drop of 2 lines or more occurred; only 5 had a final acuity of 6/12 or better. The drop of visual acuity coincided with flattening without any intervening event such as haemorrhage. In patients with visual loss the central retinal pigment epithelium appeared relatively normal (Fig. 4), but stereoangiography, when available, showed thinning of the central neuroretina. The fovea was not photocoagulated in any patient and the smallest distance between the foveola and a photocoagulation lesion was 150 μm.

Of the 4 with a vascular disciform lesion at the end of the period of observation, subretinal new vessels were evident within 2 weeks of initial photocoagulation in 2 cases; further treatment failed to destroy these vessels. In the other 2 cases the retinal pigment epithelium flattened rapidly after initial photocoagulation; in one a new disciform lesion occurred elsewhere in the posterior pole after 4 months and in the other subretinal new vessels grew from the edge of the previous detachment at 6 months. All 4 had poor acuity at the end of the study.

Both patients with persistent detachment of the retinal pigment epithelium had small subfoveal lesions, and it was thought that further photocoagulation might prejudice foveal function; one retained good visual acuity and in one there was deterioration from 6/18 to 6/36.

UNTREATED PATIENTS

Of the 24 untreated patients seen at 18 months 12 had persistent detachment of the retinal pigment epithelium, 3 had spontaneous flattening of the pigment epithelium, and 6 had a disciform lesion. In the remaining 3 a tear of the pigment epithelium developed during the first year after entry into the trial.

Two of the patients with subretinal neovascularisation had severe loss of visual acuity, and one had poor acuity on entry to the trial. The remaining 3 retained good vision (6/18 or better); in these, new vessels could be seen beneath an apparently intact retinal pigment epithelium (Fig. 5).

Of the 12 with persistent detachment of the retinal pigment epithelium 11 retained good visual acuity, and in only 3 did the acuity become worse that 6/18.

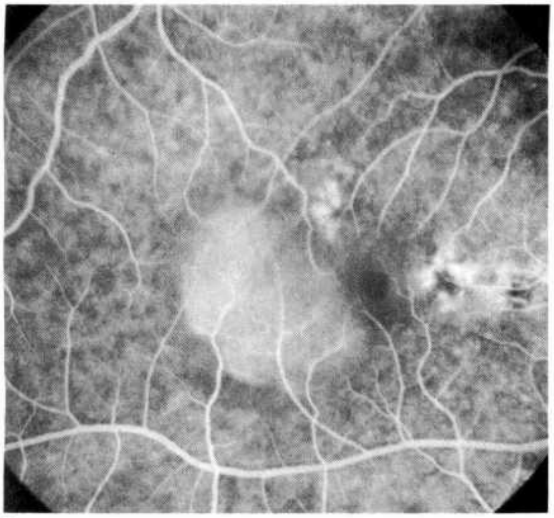
Flattening of the pigment epithelium was associated with good visual acuity. In each patient with a tear in the pigment epithelium severe loss of vision occurred soon after the tear.

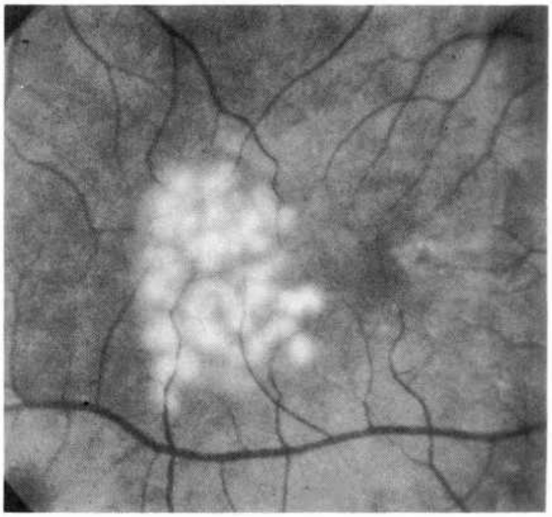
Discussion

Three aspects of clinical behaviour during the trial were unexpected. It was disappointing that the high success rate in achieving pigment epithelial and retinal flattening was not accompanied by improvement of vision and maintenance of the initial visual acuity. The reason for the loss of vision is not clear, although the evidence suggests that poor vision was due to loss of foveal neuroretina. The central retinal atrophy was not due to direct coagulation of the foveola, but it is possible that photoxic damage might have occurred at the foveola due to scattered irradiation from the parafoveal burns. Alternatively, if there was significant absorption of argon laser energy by the luteal pigment in the neuroretina, the functional loss may have been caused by destruction of parafoveal neurones subserving foveal function[21]; this effect should be avoided by using the krypton laser.[22]

The retention of good acuity in half the untreated patients with subretinal neovascularisation is in marked contrast to the reported behaviour of disciform macular disease in the elderly and treated patients in this trial. Clinical observations during this period of the trial suggest that, in those who maintained good vision, the subretinal blood vessels proliferated on the inner surface of Bruch's membrane without destroying the integrity of the pigment epithelium. However, when there is rapid growth of vascular tissue within a disciform lesion in the absence of prior pigment epithelial detachment, it appears that the pigment epithelium becomes incorporated within the fibrovascular tissue in the early stages. In the first case the metabolic relationship between the pigment epithelium and retinal receptors would be relatively unaltered, whereas in the second it would be disrupted. The original assumption was that the main complication of pigment epithelial detachment was subretinal neovascularisation, which was inevitably followed by loss of visual acuity; clearly this assumption should be reconsidered.

The phenomenon of tearing of detached pigment epithelium was described only recently and was unrecognised at the start of the trial.[23] The results suggest that the incidence of tearing was not increased by photocoagulation but that treatment causes it to


2a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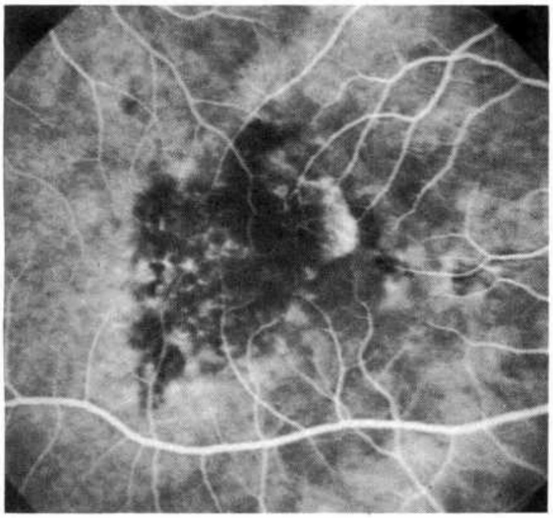
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Fig. 2 (a) *Pigment epithelial detachment with hyperfluorescence, but no leakage, upper nasal to, and remote from, the lesion;* (b) *treatment;* (c) *development of a vascular disciform lesion remote from the treated and flattened detachment.*

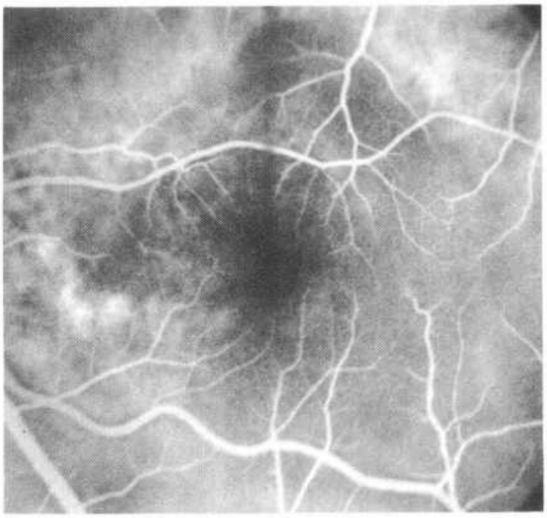
occur earlier than it might otherwise have done. The visual morbidity of pigment epithelium tearing was greater than subretinal neovascularisation in the individual patient. The number of patients losing vision from each of these complications was similar in the treated and untreated groups.

It is also evident that persistent detachment of the pigment epithelium in the elderly is compatible with retention of good visual acuity.

Various factors contribute to render the trial negative with respect to photocoagulation during the first 18 months after entry. The most important were the loss of vision in the treated patients with retinal pigment epithelial flattening and pigment epithelial tearing, and the retention of acuity in most untreated patients with persistent detachment and in some with subretinal neovascularisation. These factors combined to render the trial negative with respect to photocoagulation.

3. REVIEW OF ENTRY CRITERIA

In this study regular reviews of photocoagulation records ensured uniformity of treatment. However



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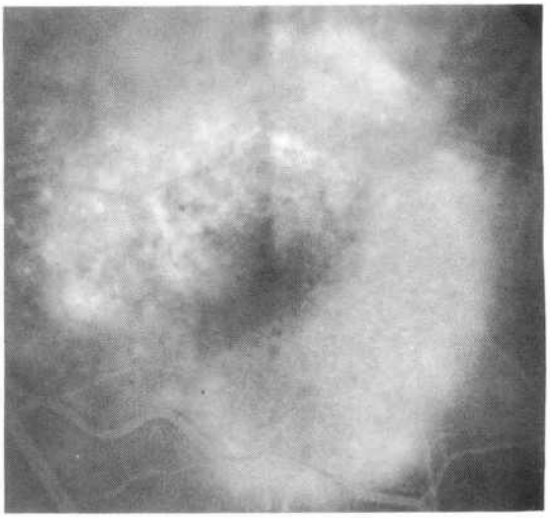

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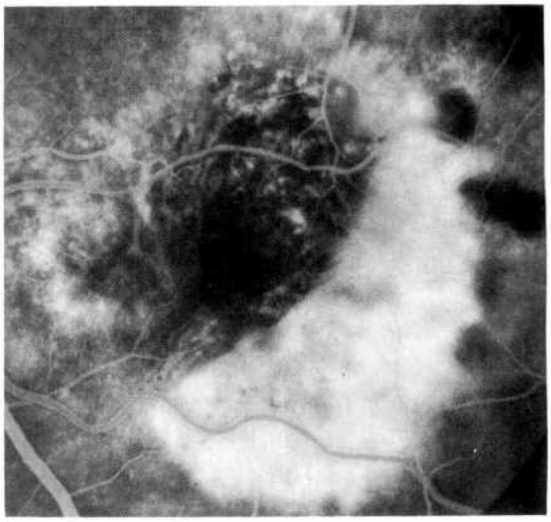


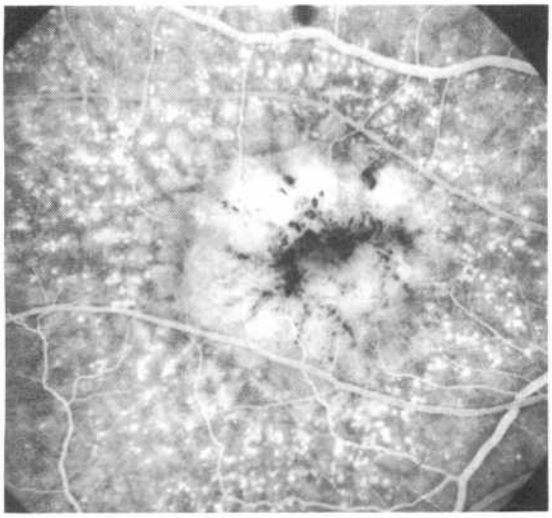
3c

Fig. 3 (a) *Pigment epithelial detachment with slow filling early in the angiogram;* (b) *in the late pictures there is even fluorescence temporally in contrast to the irregular transmission nasally;* (c) *tearing of the pigment epithelium seen 1 month following photocoagulation.*

the validity of any trial of therapy may also be questioned on the basis of patient selection or treatment technique. Every effort was made to prevent inclusion of lesions with subretinal neovascularisation, but there was sometimes doubt as to the nature of lesions at the time of entry.[6]

The original criteria for entry into the trial specifically excluded those lesions in which there was evidence of haemorrhage or exudate beneath the neurosensory retina or pigment epithelium, and those containing localised and increasing subretinal hyperfluorescence. Delayed but even hyperfluorescence of the detachment and uneven hyperfluorescence may indicate masking by debris under the pigment epithelium, and such cases were interpreted with care. They were not specifically excluded, since these variations do not inevitably imply the presence of subretinal new blood vessels.

Recently it has been suggested that the clinical appearance of a pigment epithelial detachment may be determined by the plane of cleavage between the retinal pigment epithelium and Bruch's membrane.[23] Detachment of the pigment epithelium with its basement membrane and associated debris gives rise to



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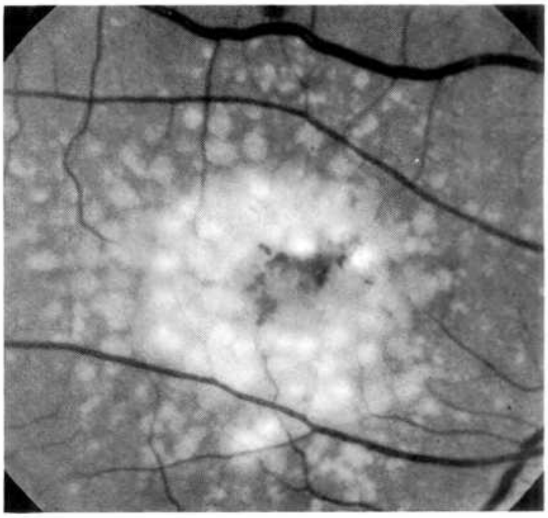

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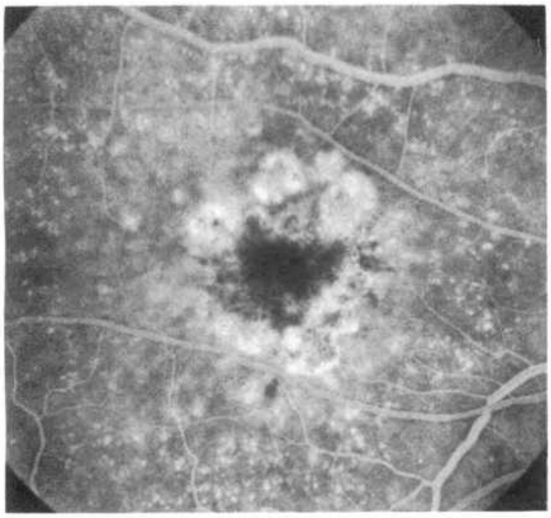


4c

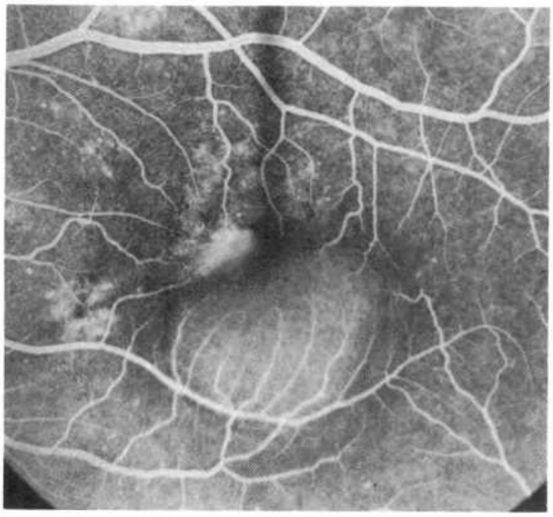
Fig. 4 (a) *Detachment with pigment figures on its surface;* (b) *grid photocoagulation sparing fixation;* (c) *flattened detachment with 1·5/60 visual acuity. The central pigment epithelium appears relatively normal, but is seen to be thin on stereoangiography.*

irregular hyperfluorescence due to uneven transmission of light by the detached tissues. By contrast in detachment of the pigment epithelium alone the fluorescein accumulates slowly and evenly. These observations may explain the variable appearance of pigment epithelial detachments.

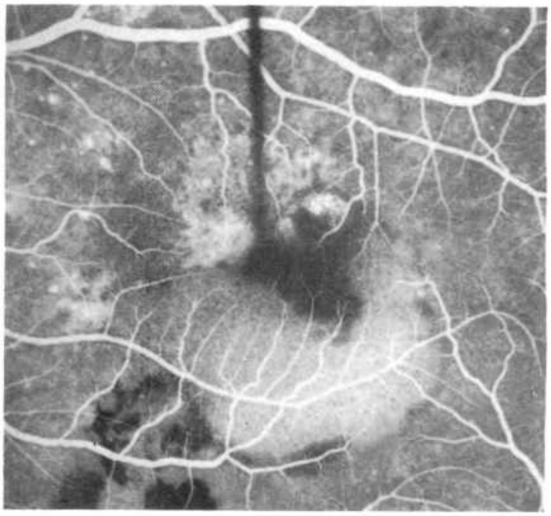
At the end of the study the initial angiograms were reviewed, and the results of the study were reanalysed to establish whether they would have been affected by revision of the entry criteria. The new criteria were designed to distinguish between irregular transmission of fluorescence by the pigment epithelium and focal hyperfluorescence within the subpigment epithelial space, and to assess the effect of excluding the patients with slow but even filling of the detachment.

Materials and methods

The entry films were studied retrospectively by 4 of the workers in the study who were masked from knowledge of the outcome. The films were assessed according to the original and to revised exclusion criteria which were (Fig. 6): (1) local progressive



5a



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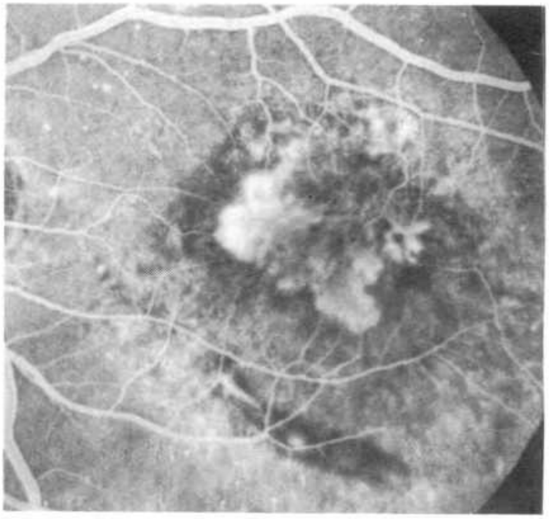


5c

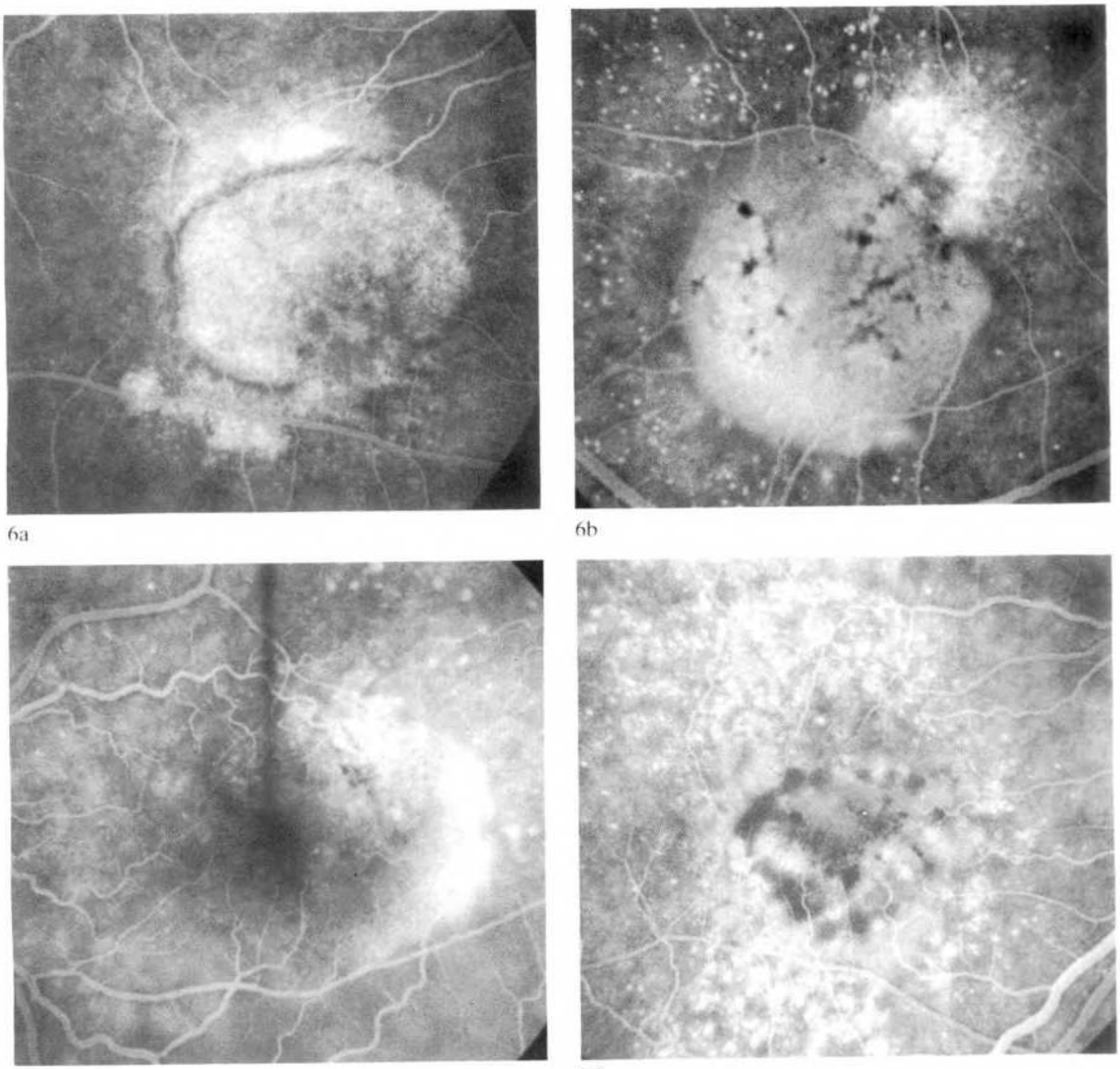
Fig. 5 (a) *Untreated pigment epithelial detachment with hyperfluorescence superiorly;* (b) *9 months later there are subretinal and subpigment epithelial haemorrhages, with further hyperfluorescence above and enlargement of the detachment;* (c) *spontaneous flattening of the detachment with evidence of a vascular disciform lesion.*

hyperfluorescence beneath the pigment epithelium, as distinct from a transmission defect or dye accumulation within detached drusen; (2) regional masking not explained by irregular transmission at the level of the pigment epithelium due to hyperpigmentation; (3) late but even filling of the detachment after the arteriovenous phase.

The conclusions were pooled, and in those in which there was not agreement, a consensus was achieved following open discussion. The statistical results were re-examined to establish whether revision of the entry criteria might have influenced the conclusions.

Results

Twenty-two patients had been entered into the treatment group of the trial. The fluorescein angiograms of 2 of these patients were not available for retrospective study. Of the remaining 20, 1 was not considered to have satisfied the original entry criteria because of an area of hyperfluorescence within the pigment epithelial detachment. On analysis of the angiograms 10 (50%) were considered to have satisfied the revised criteria and 10 were not. (In 10 there was uniformity of opinion on masked assessment as to



6a

6b

6c

6d

Fig. 6 (a) *Detachment showing hyperfluorescence in detached drusen on its posterior surface, without deep focal fluorescence on stereoangiography;* (b) *detachment showing regional masking due to hyperpigmentation on its surface;* (c) *detachment with delayed filling after the arteriovenous phase;* (d) *detachment with late filling after the arteriovenous phase, some deep masking in addition to surface pigment, and deep progressive hyperfluorescence seen on stereoangiography.*

their classification status, and in the remaining cases reclassification was made after open discussion.)

Of the 27 patients admitted to the untreated group 1 was considered not to have fulfilled the original entry criteria. Sixteen (61·5%) eyes were thought to have satisfied the revised criteria and 10 were not. (There was initial agreement about the classification status of 9 eyes and reclassification in the remainder was achieved after discussion.)

Nine patients developed vascular disciform lesions within the pigment epithelial detachment; only 3 of these would have been excluded by the revised criteria.

None of the 5 eyes that sustained tears of the pigment epithelium satisfied the revised criteria. Four had delayed but even filling of the detachment, and the fifth had regional masking within the subpigment epithelial space. With the exception of pigment epithelial tears there was no correlation between the morphological outcome and the classification according to the revised criteria (Tables 7–11).

It is evident that the visual outcome in the 2 groups is similar to that in the main trial; in both, the treated patients fared worse than the untreated in terms of visual function.

Discussion

The revised criteria attempted to exclude any pigment epithelial detachment that demonstrated late filling after the arteriovenous phase on fluorescein angiography. Delayed filling may be due to opacity or turbidity of the subpigment epithelial fluid masking neovascular tissue present deep to that fluid. Alternatively, if the pigment epithelium detaches without its basement membrane, this structure, which remains attached to Bruch's membrane, may act as a barrier to diffusion of the fluorescein, and so delay the entry of dye into the subpigment epithelial space. It is reported that this type of pigment epithelial detachment may sustain a tear of the pigment epithelium[23] and it is notable that in 4 out of 5 of those cases in which this occurred slow filling of the detachment was demonstrated. However, retinal pigment epithelial tearing accounted for only 2 of the 8 treated patients

Table 7 *Number of patients who had completed the indicated visit by 30 September 1980, broken down by suitability for study*

Visit	*Group*			
	Treated		*Untreated*	
	Suitable	*Doubtful*	*Suitable*	*Doubtful*
Initial	10	9	16	9
3 months	10	9	16	9
6 months	9	7	16	9
9 months	8	8	16	8
12 months	8	9	16	9
18 months	8	9	15	9

Table 8 *Number and percentage of patients whose visual acuity deteriorated between the initial visit and the visit indicated, broken down by suitability for study*

A: Taking a move of one or more lines as a change

Visit	*Group*							
	Treated				*Untreated*			
	Suitable		*Doubtful*		*Suitable*		*Doubtful*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
3 months	5	56	9	90	3	20	1	14
6 months	7	88	6	75	6	43	2	29
9 months	6	75	7	78	6	43	3	50
12 months	6	75	8	80	6	43	4	57
18 months	6	75	8	80	7	50	6	86

B: Taking a move of two or more lines as a change

3 months	3	33	4	40	2	13	0	0
6 months	4	50	4	50	1	7	1	14
9 months	4	50	4	44	2	14	1	17
12 months	5	63	6	60	3	21	1	29
18 months	6	75	8	80	6	43	3	43

Table 9 *Number of lines moved on Snellen chart since initial visit, broken down by suitability for study*

Visit	*Group*							
	Treated				*Untreated*			
	Suitable		*Doubtful*		*Suitable*		*Doubtful*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
3 months	−2·2	3·1	−2·1	1·8	−0·1	1·0	0	0·6
6 months	−3·6	3·0	−2·3	3·0	−0·2	1·1	−0·3	0·9
9 months	−3·0	3·0	−2·8	3·1	−0·4	0·9	−0·8	1·7
12 months	−3·3	2·9	−3·0	2·7	−0·6	1·4	−1·4	2·4
18 months	−3·1	2·8	−3·2	2·6	−1·4	2·5	−2·1	2·7

Table 10 *Number and percentage of patients who had visual acuity less than the specified end-point at one or more visits and had completed the visit indicated, broken down by suitability for study*

A: 6/36

Visit	*Group*							
	Treated				*Untreated*			
	Suitable		*Doubtful*		*Suitable*		*Doubtful*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
3 months	4	40	2	22	2	13	0	0
6 months	5	56	2	29	2	13	0	0
9 months	4	50	3	38	2	13	1	13
12 months	4	50	4	44	2	13	2	22
18 months	4	50	4	44	4	27	2	22

B: 6/60

3 months	2	20	1	11	0	0	0	0
6 months	3	33	2	29	0	0	0	0
9 months	2	25	3	38	0	0	0	0
12 months	2	25	3	33	1	6	1	11
18 months	2	25	3	33	2	13	2	22

Table 11 *The change in field scores from the initial visit to the visit indicated, broken down by suitability for study*

Visit	*Group*							
	Treated				*Untreated*			
	Suitable		*Doubtful*		*Suitable*		*Doubtful*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
A: Error total								
3 months	−12·8	42·9	−24·8	65·2	−17·2	45·0	−19·1	32·4
6 months	9·4	48·4	−35·0	124·1	−9·2	74·9	−44·0	112·1
9 months	29·1	50·9	−50·2	97·1	−28·8	91·1	−81·7	128·7
12 months	7·4	65·4	−58·2	90·2	−44·8	110·3	−85·3	93·4
18 months	−3·7	51·7	−62·2	99·4	−21·3	69·2	−73·4	130·0
B: Error Central								
3 months	−21·5	20·4	−19·2	25·5	−5·7	24·5	−4·3	8·0
6 months	−11·7	27·1	−16·8	37·7	−8·5	30·7	−13·4	36·3
9 months	−5·9	24·7	−27·4	31·0	−17·1	31·8	−47·0	47·0
12 months	−13·7	31·0	−32·4	25·7	−25·8	47·3	−34·3	33·6
18 months	−26·0	15·7	−34·8	24·2	−23·7	33·0	−37·4	49·3
C: Missed total								
3 months	3·1	4·4	1·1	4·1	−0·6	5·7	2·9	6·5
6 months	3·6	4·1	−2·6	9·1	0·1	6·5	5·0	4·8
9 months	0·7	5·1	0·7	5·9	2·0	6·9	5·2	10·6
12 months	1·0	7·3	1·7	4·9	2·3	6·8	7·6	6·1
18 months	3·3	4·9	3·0	7·2	2·7	5·9	7·7	7·0
D: Missed central								
3 months	1·6	0·7	2·8	2·9	0·7	1·5	0·1	0·4
6 months	2·1	1·6	2·1	3·0	0·5	1·4	0·0	0·0
9 months	1·7	1·3	2·7	3·7	0·5	1·1	3·8	4·4
12 months	2·1	2·0	3·6	3·3	1·3	3·1	3·0	4·0
18 months	3·0	1·6	3·4	2·5	1·3	2·6	4·1	4·1

with visual loss, so that exclusion of these 2 patients would not have affected the findings of the trial.

Regional masking within a detachment was frequently a difficult sign to interpret. Importance was attached to the difference between masking caused by haemorrhage or exudate within the subretinal space, indicating possible neovascularisation, and that associated with local hyperpigmentation over the surface of the detachment. This distinction required high-quality stereoscopic angiograms, which may be hard to obtain in the elderly patient, and their comparison with colour photographs.

There was similar difficulty in making the distinction between the hyperfluorescence caused by detached drusen or pigment epithelial defects, and that of neovascular tissue beneath the pigment epithelium. In lesions in which the pigment epithelium detaches with its basement membrane and drusen, there may be focal and increasing hyperfluorescence, which is not always easy to differentiate from hyperfluorescence due to subpigment epithelial new vessels.

The problems of interpretation are reflected in the fact that an initial consensus of opinion as to whether a particular lesion fulfilled the revised entry criteria was achieved in only 40% of the cases. Nevertheless, it is clear that revision of the entry criteria would not have influenced the results or the conclusions drawn from this trial.

This study was supported in part by the Medical Research Council grant no. G976/618, and by the National Institute of Health, Washington, grant no. 5 RO1 Ey02168-02.

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British Journal of Ophthalmology, 1982, **66**, 17–25

A new perspective on Bruch's membrane and the retinal pigment epithelium*

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SUMMARY Trypsin digestion of retinal pigment epithelium is a technique that bares Bruch's membrane, to allow topographical examination by scanning electron microscopy. Twenty-five human eyes were examined. The zonula occludens of the pigment epithelium was clearly seen as a surface feature, but attachment plaques at the sides and base were not visible. The adhesion between the pigment epithelium and the basal lamina was stronger than between the basal lamina and the rest of Bruch's membrane. Surface features of the basal lamina, inner collagenous zone, elastic layer, and outer collagenous zone were seen in a way that previously required an artist's representation constructed from microscopic sections.

Since 1844, when Karl Bruch described a 'structureless membrane' between the retina and choroid,[1] almost all anatomical examinations have been by light microscopy or transmission electron microscopy.[2-9] Most of these histological and electron microscopic sections were cross-sections or tangential sections through the membrane, which we describe today as having 5 components: (1) basal lamina of the pigment epithelium; (2) inner collagenous layer; (3) elastic layer; (4) outer collagenous layer; and (5) basal lamina of the choriocapillaris, where it is present.

A technique was devised to loosen enzymatically pigment epithelium from Bruch's membrane to allow evaluation of surface features by scanning electron microscopy, thereby offering a perspective view of Bruch's membrane and its component layers. This technique also demonstrates surface features of pigment epithelium that have not been demonstrated previously. Scanning electron microscopy allows conceptualisation of 3-dimensional structure in a way that sections cannot. In this report the surface features of Bruch's membrane and parts of the retinal pigment are described. In separate reports the same techniques will be used to evaluate regional variations, drusen, and aging changes in Bruch's membrane.

Methods and materials

Twenty-five eyes were obtained from the eye bank and placed in chilled buffered glutaraldehyde 1% and paraformaldehyde 1% (buffered to pH 7·45 with 0·1 M monobasic and dibasic phosphate) between 50 minutes and 3 hours 25 minutes after death. The corneas of most of the eyes were removed prior to fixation. The donors ranged in age from 15 to 83 years.

After fixation the eyes were sectioned coronally through the equator. Each calotte was examined with the stereoscopic microscope for drusen, pigment changes, and other abnormalities. Three specimens were obtained with trephines. A specimen containing the disc and macular region was obtained with an 8·5 mm trephine. A specimen at the equator and a specimen straddling the ora each were obtained with a 6 mm trephine.

To help localisation of the region under the fovea the piece containing disc and macula was notched at the edge superior and inferior to the fovea. The sensory retina was removed, and each piece was photographed.

After the retina was removed each trephined piece was digested in buffered bovine pancreas trypsin 0·5% (Sigma) for 40 to 60 minutes at 37°C. The trypsin was buffered to pH 7·25 with 0·1 M Tris maleate buffer in 0·02% ethylene diamine tetra-acetic acid. The retinal pigment epithelium was washed off Bruch's membrane with a stream of phosphate

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*Presented in part at the Association for Research in Vision and Ophthalmology, Sarasota, Florida, 4 May 1979.

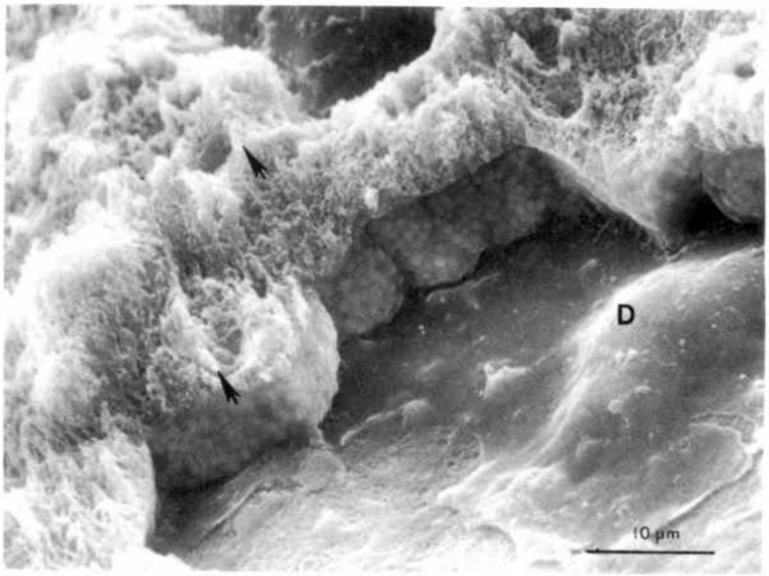

Fig. 1 *Scanning electron microscopy of pigment epithelium showing smooth side walls and microvilli on inner surface. Pockets in microvilli surrounded rods. Microvilli at border of pockets (arrow) mat together to form ridges that surround tip of rod.* D=*druse*. (× *1745*).

buffer from a pipette (0·1 M monobasic and dibasic phosphate at pH 7·45). The specimen was then postfixed in osmium tetroxide 2%.

For scanning electron microscopy a specimen was dried in a critical-point bomb, coated with gold and palladium, and examined by mapping at progressively increasing magnification. For transmission electron microscopy only, a specimen was dehydrated in increasing concentrations of ethanol, mounted in Epon 812, thin-sectioned, and stained with lead citrate and uranyl acetate. Some specimens were examined by correlated scanning and transmission electron microscopy of the same piece. After a specimen was examined by scanning microscopy it was placed in ethanol 100%, then mounted in Epon 812 for thin sectioning and staining.[10] Other pieces were cut in half for separate processing for scanning electron microscopy and transmission electron microscopy.

Results

PIGMENT EPITHELIUM

The digestion process loosened most of the pigment epithelium from Bruch's membrane; irrigation with

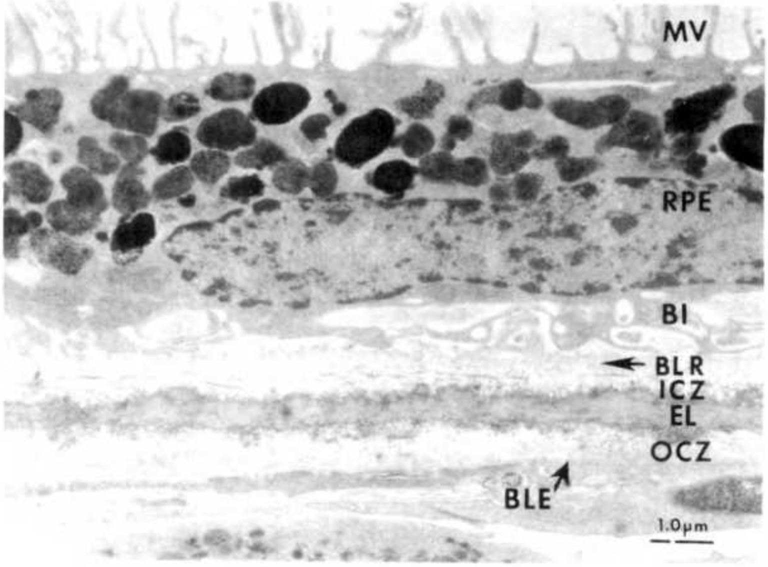

Fig. 2 *Transmission electron microscopy of pigment epithelium and Bruch's membrane.* MV=*microvilli*, RPE=*pigment epithelium*, BI=*basal infolding*, BLR=*basal lamina of pigment epithelium*, ICZ=*inner collagenous zone*, EL=*elastic lamina*, OCZ=*outer collagenous zone*, BLE=*basal lamina of endothelium of choriocapillaris*. (× *8290*).

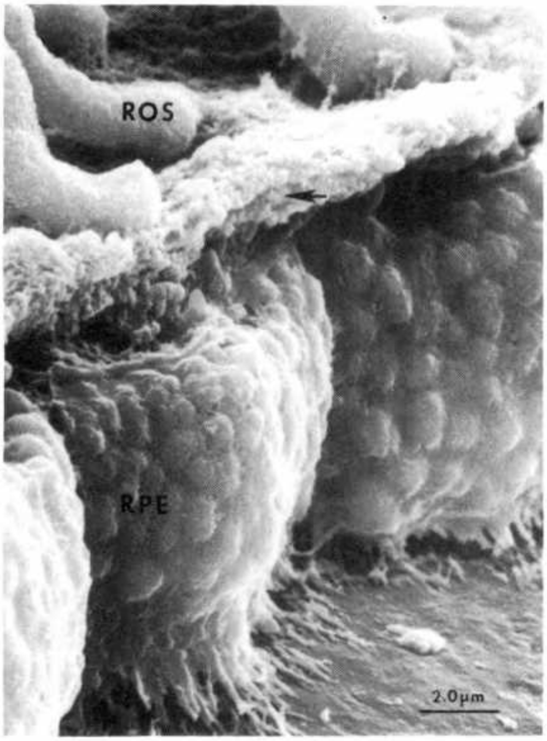

Fig. 3 *Rods inserting into plate of material on apical surface of retinal pigment epithelium (arrow).* ROS = *rod outer segment. (Magnification* = × *5965).*

phosphate buffer exposed broad expanses of Bruch's membrane. Patches of pigment epithelium remained attached to Bruch's membrane.

Microvillous processes extended from the apex of the pigment epithelial cells (Figs. 1 and 2). In most of the specimens the retina completely separated from the pigment epithelium, leaving pockets where the outer receptors of the rods had been. The microvilli were long and hair-like between these pockets.[11] At the border of the pockets the villous processes appeared matted together or took the form of a ridge partially wrapped around the pocket. In some specimens the villous processes were covered with a material, presumably the mucopolysaccharides between outer receptors and the pigment epithelium. This material appeared as a plate with spaces for the receptors (Fig. 3).

The site of the zonula occludens was visible as a band about 500 nm wide encircling each pigment cell at the junction between the apex and the sides (Fig. 4). In most specimens this band was a flat outpouching of the cell membrane at the sides of the pigment cell. In other specimens this band appeared to shrink from processing more than the sides of the cell, which sometimes bulged above the band.

The zonula adherens and the maculae adherentes were not visible on the sides of the pigment epithelium by scanning electron microscopy. The smooth cell membrane on the sides of the pigment epithelium bulged over the melanin granules (Fig. 1).

The basal surface of the pigment epithelium was generally not visible from the outside. In one specimen a sheet of remaining pigment epithelium was detached from the basal lamina and curled

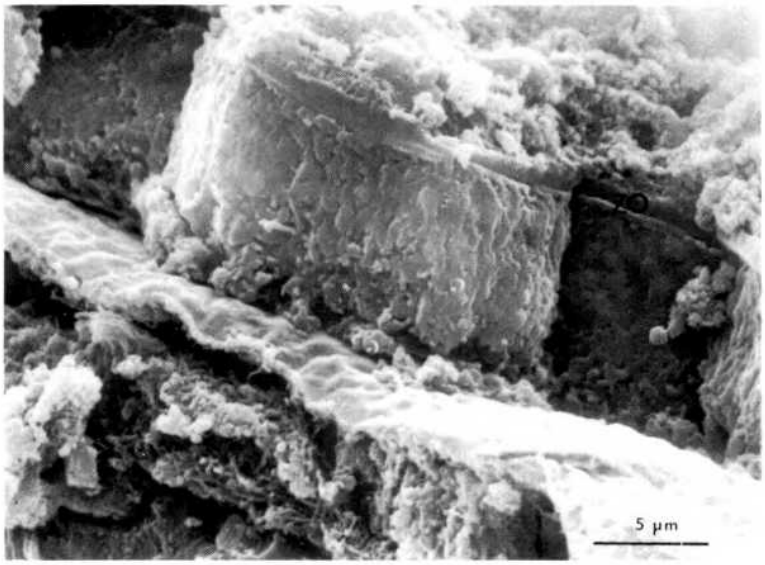

Fig. 4 *Pigment epithelium with a band at site of zonula occludens* (ZO) *surrounding each cell at junction between sides and apex. The sides show some deterioration from exposure to trypsin.* (× *3117*).

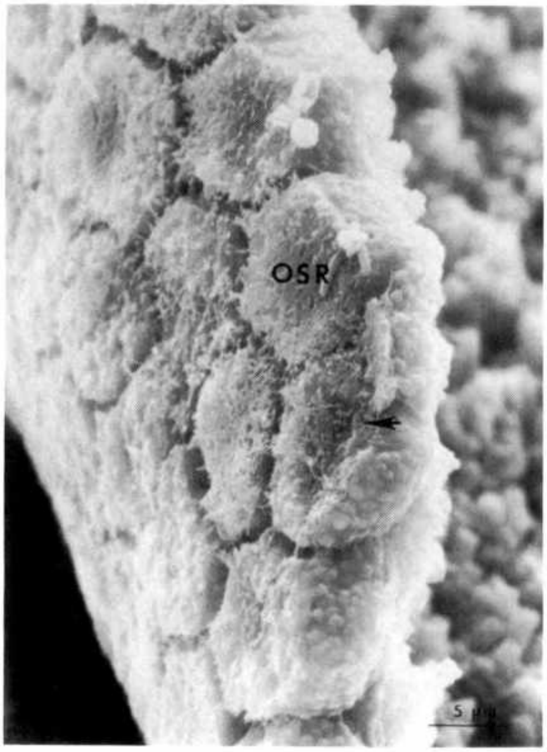

Fig. 5 *Sheet of pigment epithelium that has peeled up from basal lamina. An amorphous material coats outer surface of pigment epithelium* (OSR). *Some basal infolding is visible (arrow). (× 2147).*

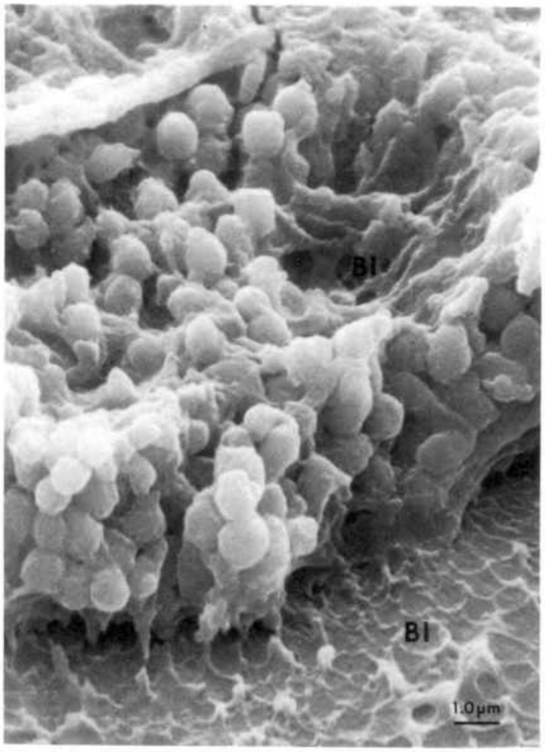

Fig. 6 *Partially digested pigment epithelium. Remnant basal infoldings* (BI) *on the basal lamina show that adhesion between basal lamina and basal infolding was stronger than integrity of cell in this eye. (× 5965).*

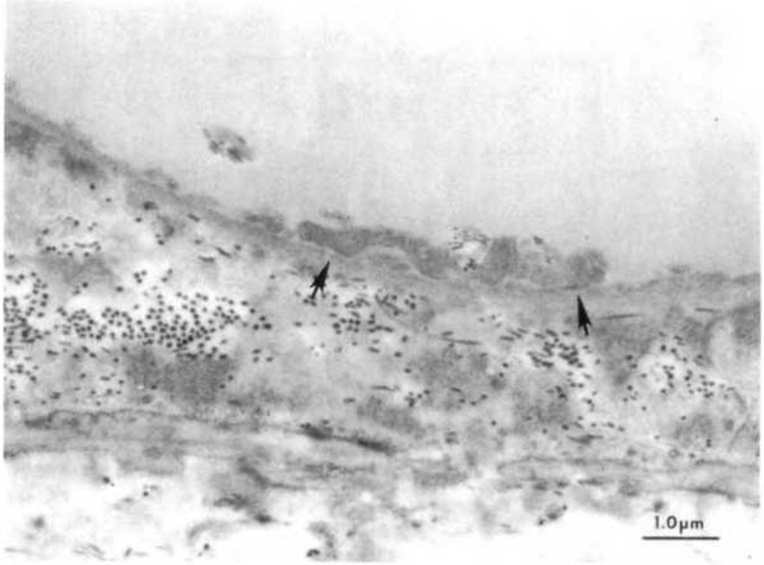

Fig. 7 *Remnants of basal infoldings attached by attachment plaques (arrow) to pigment epithelium. (× 10 286).*

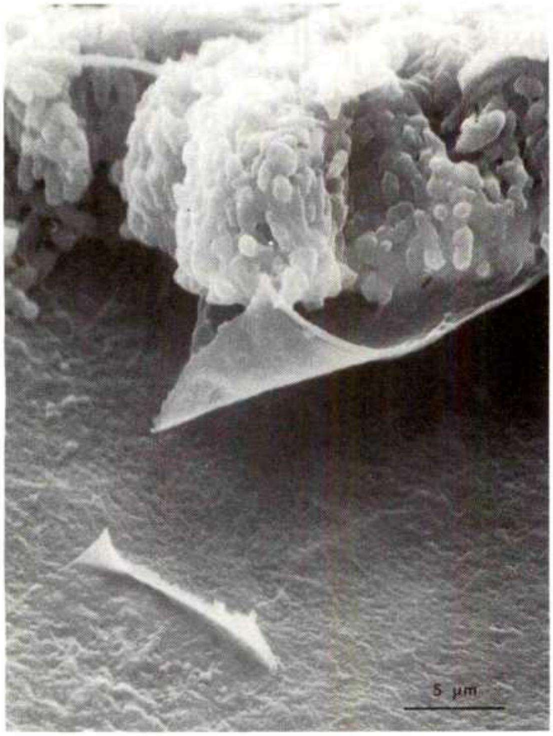

Fig. 8 *Basal lamina peeling away from inner collagenous zone. At low power basal lamina appears like a plastic membrane.* (× *2684*).

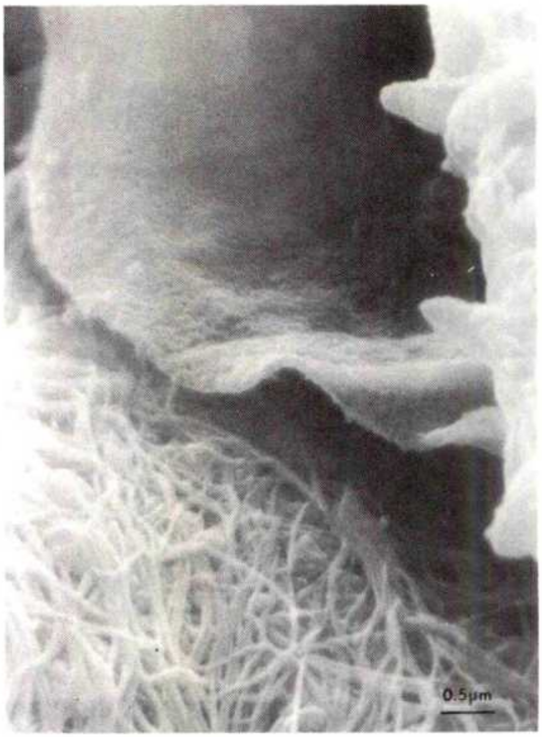

Fig. 9 *Basal lamina at high magnification appears granular or velvety.* (× *14316*).

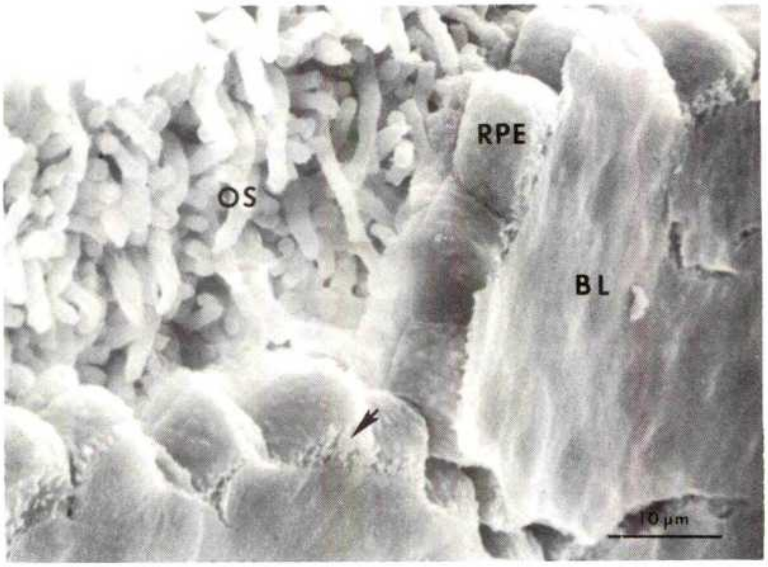

Fig. 10 *Detachment of pigment epithelium* (RPE) *exposing outer surface of basal lamina* (BL) *much in the manner of a clinical retinal pigment epithelial detachment. Note amorphous material between pigment epithelium and basal lamina (arrow). No attachment sites are visible between basal lamina and inner collagenous zone. In this specimen the retina remains, exposing outer segment* (OS). (× *1496*).

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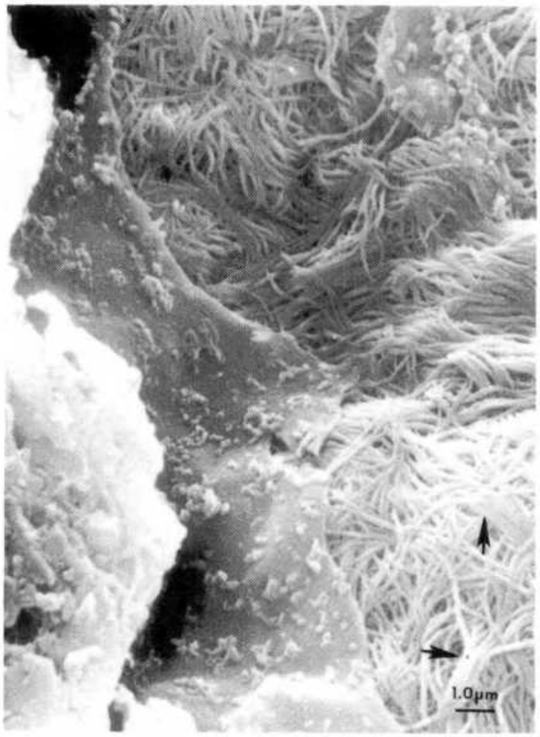

Fig. 11 *Where basal lamina is absent, the inner collagenous zone is visible, revealing tight interweaving of collagen fibres. The fibres occasionally appear joined together lengthwise (arrow). (× 5368).*

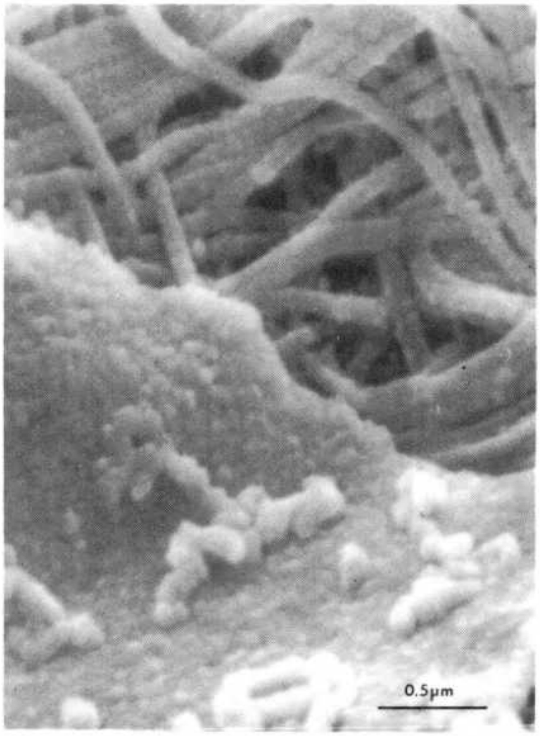

Fig. 12 *With high magnification the fibres of the inner collagenous zone appear to have an external representation of banding. (× 29 825).*

inwards. An amorphous material adhered to the external surface, leaving clefts where basal infolding was present (Fig. 5).

PIGMENT EPITHELIUM ADHESIONS TO BRUCH'S' MEMBRANE

In many specimens the adhesion of the basal cell membrane to the basal lamina of Bruch's membrane was stronger than the integrity of the cell, leaving remnant basal cell membrane on the basal lamina. The internal aspect of this remnant membrane showed basal infolding (Fig. 6). Transmission electron microscopy of the same piece showed attachment plaques of the flat parts of the cell basal membrane to the basal lamina (Fig. 7).

Broad expanses of the basal lamina were completely bared following enzymatic digestion and irrigation. The inner surface of the basal lamina was smooth and showed no evidence of the location of attachment plaques of pigment epithelium (Figs. 8 and 9).

BRUCH'S MEMBRANE

Four of the 5 layers of Bruch's membrane were observed by scanning electron microscopy. The process of enzymatic digestion and irrigation exposed most of Bruch's membrane. 25 to 50% of the basal lamina was lost from each specimen, allowing easy visualisation of the inner collagenous zone. The rest of Bruch's membrane generally remained intact. The shrinkage produced by the critical-point processing caused the edges of some specimens of Bruch's membrane to curl inwards, allowing visualisation of the elastic layer and the outer collagenous layer. The basal lamina of the choriocapillaris endothelium was not seen.

Basal lamina of the pigment epithelium. By transmission electron microscopy the basal lamina showed as a straight, finely-granular membrane 40 to 100 nm thick (Fig. 1). Its appearance by transmission electron microscopy did not prepare one for its appearance by scanning electron microscopy. With moderate magnification the basal lamina appeared like a smooth thin plastic membrane (Fig. 8). At high magnification, the membrane took on a more granular appearance (Fig. 9). Both surfaces were smooth. There was no visible evidence on the inner surface where pigment epithelial attachments were located. There was no evidence of

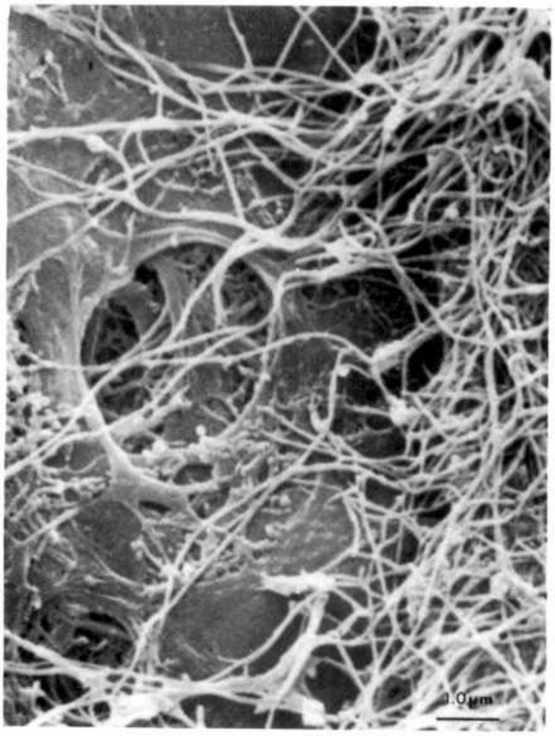

Fig. 13 *Elastic lamina with some collagen fibres lying on inner surface. Some of inner collagen fibres are inserted into elastic layer and some join outer collagenous layer by passing through holes in elastic lamina.* (× 8350).

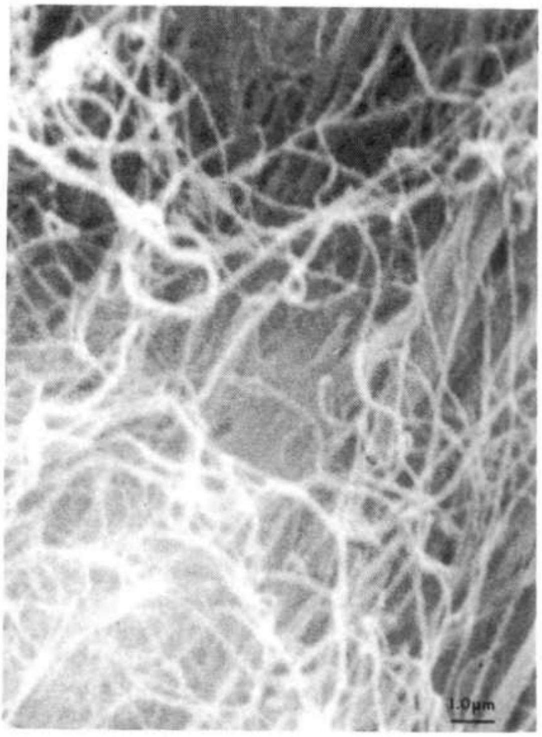

Fig. 14 *Curling up of part of Bruch's membrane has exposed outer collagenous layer. The collagen fibres are less tightly woven.* (× 5276).

insertion of collagen fibrils from the inner collagenous layer into the basal lamina (Fig. 10). The basal lamina tended to separate easily from the inner collagenous layer; the attachment between the basal lamina and the inner collagenous layer appeared to be much less firm than between the pigment epithelium and the basal lamina (Figs. 6, 10).

Inner collagenous layer. At low magnification the inner collagenous layer appeared like velvet (Fig. 8). At moderate magnification the collagen fibres in the inner collagenous layer formed a tightly interwoven membrane (Fig. 11). The ground substance between the fibres was not visible. At high magnification the collagen fibres appeared to have a uniform thickness of about 70 nm (Fig. 12). There were transverse ridges with a periodicity of about 60 nm, perhaps representing a surface manifestation of the banding seen in these fibres by transmission electron microscopy.

Elastic layer. The elastic layer appeared to be composed of coarse and fine fibres matted together by some amorphous substance (Fig. 13). This layer formed an almost solid sheet with clefts and small holes. Collagen fibres from the inner collagenous layer appeared to be inserted into the elastic layer and also to pass through holes in the elastic lamina to join with collagen fibres in the outer collagenous layers.

Outer collagenous layer. The collagen fibres in the outer collagenous layer were less dense, finer in appearance, and more loosely interwoven than those in the inner collagenous layer (Fig. 14). The collagen network between the choriocapillaries appeared similar to the outer collagenous layer, with which it was continuous (Fig. 15).

Discussion

The enzymatic loosening of the pigment epithelium allowed scanning electron microscopy of Bruch's membrane. Some of the pigment epithelium did not wash away, and the remaining cells showed variable amounts of enzyme effect, ranging from not visible to severely digested.

The microvilli around receptor elements have previously been observed by transmission electron microscopy to mat together and form ramparts.[9] The ridge we saw with scanning electron microscopy may

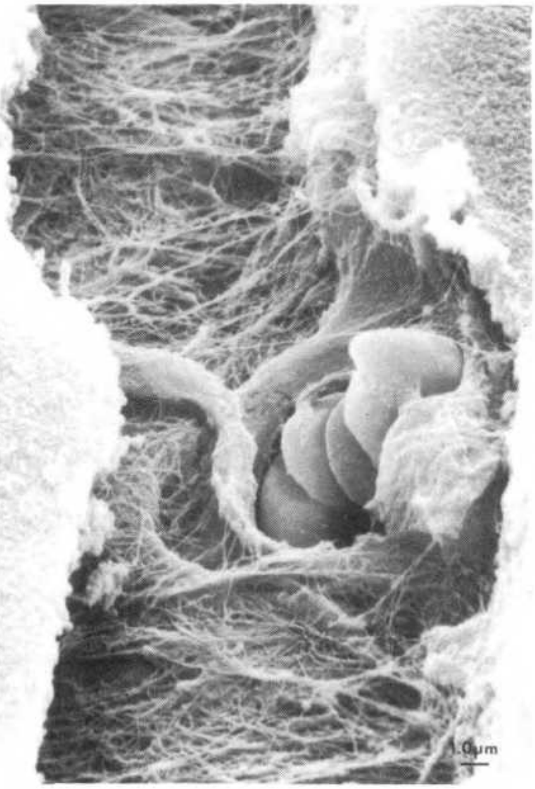

Fig. 15 *Outer collagenous layer is continuous with collagen fibres between vessels in choroid. Split in Bruch's membrane has exposed choriocapillaris and collagen fibres between. (× 3517).*

be the same feature. On the other hand there could be an enzyme artefact. Likewise the plate we sometimes observed between pigment epithelium and rods and cones could be mucopolysaccharides or could be an enzyme artefact. The zonula occludens was a surface feature visible as a band round the sides of the cell near the apex.[12 13] We believe the zonula occludens has not previously been described as a visible surface feature of the retinal pigment epithelium. It functions as an outer blood-retina barrier to large molecules.[14–16] The sides of the pigment epithelium covered the pigment granules and were otherwise smooth; attachment plaques at the sides

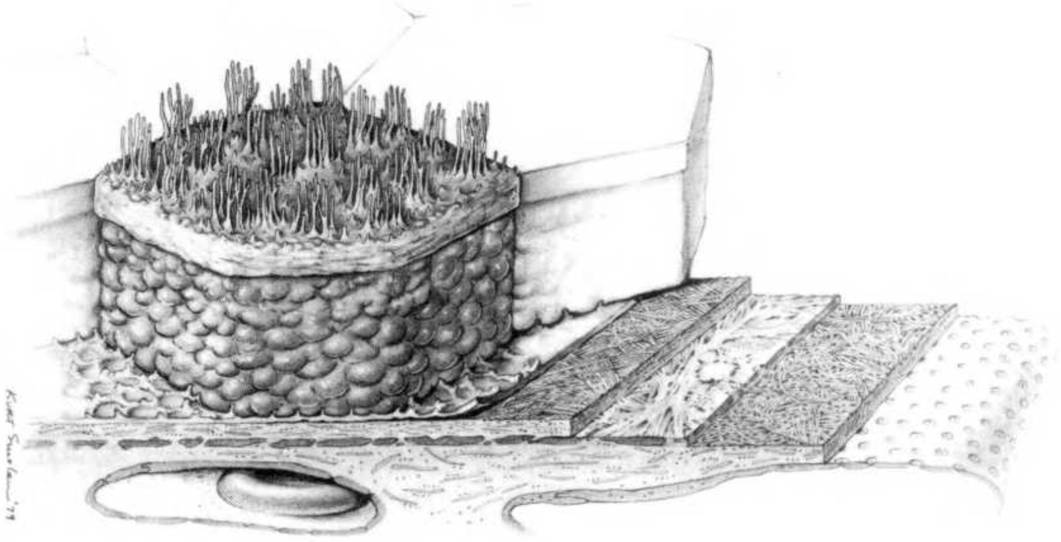

Fig. 16 *Artist's representation of pigment epithelium and Bruch's membrane. Microvilli extend from apical surface of pigment epithelium, occasionally forming pockets for rod outer segment. The zonula occludens barrier surrounds each cell, separating the side membrane and the apical surface. The basal lamina of the pigment epithelium is smooth like a thin plastic membrane. Basal infoldings adhere to basal lamina, which is not tightly attached to the inner collagenous zone. Inner collagenous fibres are more tightly woven than outer collagenous fibres. Elastic lamina forms a plate with holes between the 2 collagenous zones.*

of the pigment epithelium[17] did not produce visible changes on the surface.

The adhesion between retinal pigment epithelium and the basal lamina was stronger than between the basal lamina and the collagenous layer. This latter junction is also the site of separation for the clinical condition of retinal pigment epithelial detachment. Attachment plaques at the basal layer of the pigment epithelium were seen in transmission electron microscopy, but were not visible as surface features by scanning electron microscopy. The amorphous material observed on the outer surface of the cell basal membrane (Fig. 10) may be involved in the adhesion to the basal lamina. There was no visible mechancal attachment between the smooth outer surface of the basal lamina and the rest of Bruch's membrane (Fig. 10).

The tightly woven collagen fibres of the inner collagenous layer and the dense elastic layer by their appearance can be surmised to act as a flexible yet stable platform in 2 dimensions to support the retina, much as the plastic film base acts as a support for the emulsion in photographic film. Another function that can be hypothesised is that these layers act as a mechnical barrier that keeps the choriocapillaries away from the retina. Fig. 16 represents an artist's concept of the composite findings of scanning and transmission electron microscopy.

Dale Deg assisted in devising techniques to expose the layers in Bruch's membrane.

This work was supported in part by grant NIH EY 02434 and VA grant MRIS 3192.

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British Journal of Ophthalmology, 1982, **66**, 26–30

Preserved para-arteriole retinal pigment epithelium (PPRPE) in retinitis pigmentosa

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SUMMARY Five patients with retinitis pigmentosa (RP) with probable autosomal recessive inheritance have been identified in whom there is relative preservation of retinal pigment epithelium adjacent to and under retinal arterioles despite a panretinal degenerative process. All the patients were hypermetropic, though patients with RP tend to be myopic. This implies that there is a factor associated with retinal arterioles which locally retards the RP process in these patients. It may be appropriate to look for the PPRPE pattern in hypermetropic RP patients.

Because more specific diagnostic tests generally are not available, many retinal dystrophies have been named on the basis of distinctive retinal patterns. This has resulted in such interesting names as vitelliruptive macular dystrophy,[1] butterfly-shaped pigment dystrophy,[2] fenestrated sheen macular dystrophy,[3] and reticular dystrophy.[4] Morphological fundus patterns have also been used in referring to unusual forms of retinitis pigmentosa (RP). These include pigmented paravenous retinochoroidal atrophy,[5] helicoid parapapillary chorioretinal degeneration,[6] sector retinitis pigmentosa,[7] retinitis punctata albescens,[8] and retinitis pigmentosa sine pigmento.[9]

Morphological classification of the pigmented retinopathies is a convenient method for separating the various forms of RP clinically, and when a fundus pattern is always inherited in the same fashion it is strong evidence supporting a single disease process. However, subsequent research will have to demonstrate which morphological types consistently have the same aetiology, since difference aetiologies may give rise to the same clinical appearance. Such is the case in fundus flavimaculatus, in which autosomal recessive and dominant pedigrees have been reported,[8] thus suggesting that at least 2 different pathological mechanisms are taking place.

The purpose of this paper is to report a distinctive pattern in 5 RP patients with probable autosomal recessive inheritance. These patients, with advanced disease, have areas of preservation of the retina pigment epithelium (RPE) adjacent to and under the retinal arterioles, while there is a general loss of the RPE throughout the retina. The amount of preserved para-arteriole retinal pigment epithelium (PPRPE) varies, but it is seen most consistently in the equator and peripheral regions of the eye.

While preservation of macular RPE is commonly seen in advanced RP, this is the first time that a specific morphological pattern of RPE preservation adjacent to retinal arterioles has been reported in retinitis pigmentosa. Since 3 of the 5 patients have pedigrees consistent with autosomal recessive inheritance, and all are hypermetropic, it is likely that these PPRPE patients represent a specific form of RP.

Case reports

CASE 1

This is a 9-year-old white boy who failed his vision test in school. There was no family history of ocular problems, and consanguinity was denied. On examination his visual acuity was noted to be RE 20/30, LE 20/40. Cycloplegic refraction was RE +6·00 +1·00×75, LE +6·00 +1·00×105.

Except for a fine nystagmus the external and slit-lamp examinations were within normal limits. Fundus examination revealed pale optic discs, with moderate attenuation of the retinal vasculature.

In the areas just anterior the vascular arcades preservation of the RPE could be seen adjacent to and under the retinal arterioles (Fig. 1). This pattern was not consistent throughout the eye and appeared to be

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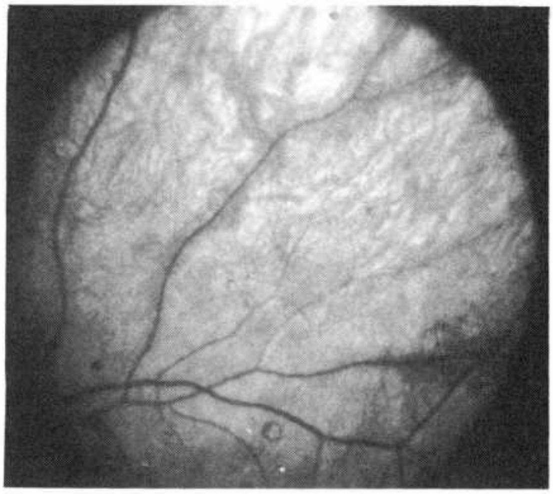

Fig. 1 *9-year-old white boy with advanced retinitis pigmentosa, showing preservation of the retinal pigment epithelium adjacent to and under retinal arteriole; left eye.*

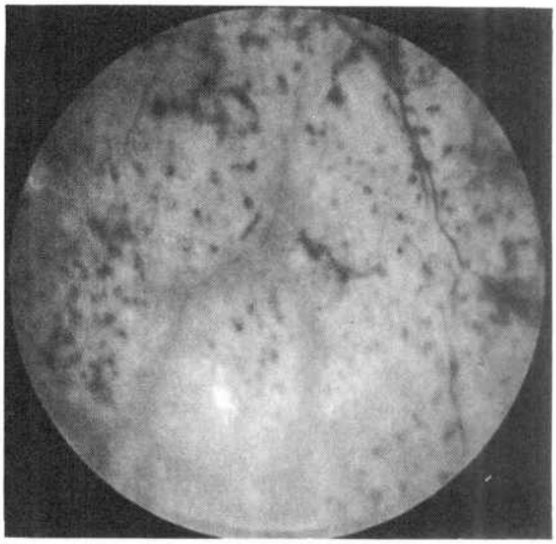

Fig. 2 *33-year-old Iranian woman with advanced retinitis pigmentosa with retinal pigment epithelium preservation adjacent to and under equator retinal arteriole. More posterior areas showed no significant preservation of retinal pigment epithelium near arterioles.*

a relative preservation. On careful review of fundus photographs patchy preservation of the RPE could be seen adjacent to smaller arterioles in the posterior pole. Round clumps of brownish-black pigment were present throughout the eye, which on stereoscopic examination were subretinal or within layers of the retina. Small yellow surface focal deposits were scattered throughout both retinas. Optic nervehead drusen were present in both eyes.

The electroretinogram performed at the referring hospital was reported to be abnormal. The dark-adaptation test with a 1° test object at 11° above fixation showed a 4·6 log unit elevation of the final rod threshold at 40 minutes. The cone threshold was also elevated, and the rod-cone break was at 17 minutes. The electro-oculogram (EOG) was abnormal, with a light-dark ratio of 100% in both eyes. The Goldmann visual field with the IV-4 isoptre was RE 30°, LE 15°.

The Farnsworth 100-hue discrimination test had a total error score of RE 191 with an early tritan axis, and LE 261 with a bipolar tritan axis. The Nagel anomaloscope had a Rayleigh equation of RE 42–50, LE 48–52, which is in the protanomalous range.

Peripheral blood smears, phytanic acid levels, vitamin A and carotene levels, quantitative haemoglobin electrophoresis, quantitative amino acids, and serology testing were all reported to be within normal limits.

CASE 2

This is a 33-year-old Iranian woman who noted night blindness at age 5 and loss of central vision at 17. The medical history was negative. The family history revealed no other member with RP, but the parents were first cousins.

On examination the patient's best corrected visual acuity was RE counting fingers, LE 4/200, with a cycloplegic refraction of RE+3·00 +0·75×120, LE +2·50. Applanation tensions and external examination were normal. Slit-lamp examination revealed bilateral posterior subcapsular cataracts. On fundus examination the optic nerve was pale, and round yellow excrescences could be seen within the nervehead substance. There was a diffuse loss of the RPE with scattered clumps of pigment at the level of the RPE. The retinal vasculature was moderately attenuated.

Preservation of the RPE could be seen next to retinal arterioles in the peripheral regions of both eyes (Fig. 2). There were localised regions where the pattern was definite, and other areas where the RPE was missing next to the arterioles. The pattern was enhanced by fluorescein angiography (Fig. 3).

An electroretinogram (ERG) was nonrecordable, and visual field study was not possible because of the advanced stage of disease. A complete blood count, fluorescent treponemal antibody test, haemoglobin electrophoresis, protein electrophoresis, quantitative amino acids, metabolic urine screen, and haemoglobin oxygenation curve were normal.

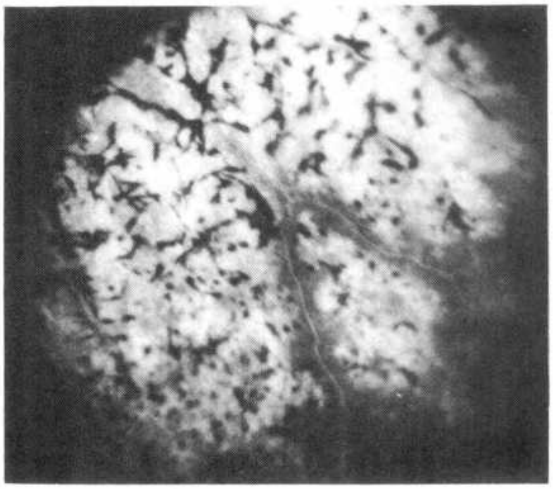

Fig. 3 *Fluorescein angiogram, case 2, confirms that the para-arteriole retinal pigment epithelium is preserved, while other retinal areas are hyperfluorescent where the retinal pigment epithelium is functionally lost.*

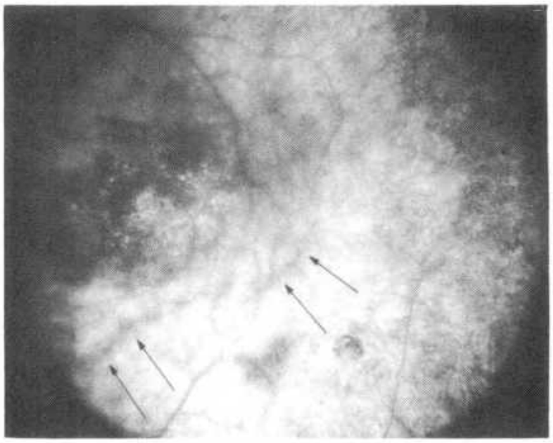

Fig. 4 *Fluorescein angiogram of 65-year-old woman with advanced RP, showing preservation of the RPE under arteriole coursing temporally inferior to macula (arrows); left eye. This pattern was not apparent on fundus examination, and it was necessary to use fluorescein angiography to confirm the PPRPE pattern.*

CASE 3

This is an 18-year-old Mexican woman with a 10-year history of nightblindness. The mother's aunt has been blind since aged 23 from unknown causes. No other family members are reported to have ocular problems, and the medical history is negative with the exception of some psychiatric problems. The patient's visual acuity was RE 20/60 with +2·00 +2·25×90, LE 20/50 with +1·50 +2·75×95. The patient had a left exotropia of 40 prism dioptres and a fine-jerk nystagmus. The right lens had a small posterior subcapsular cataract, and each eye had +2/4 pigment in the anterior vitreous.

Fundus examination revealed diffuse loss of the retinal pigment epithelium except for bilateral islands of RPE in the maculae. There was attenuation of the retinal vasculature and scattered areas of pigment deposition, with tiny drusen throughout the fundus. Optic nervehead drusen were seen on stereoscopic examination of fundus photographs. In the right eye 2 areas of distinctly preserved para-arteriole retinal pigment epithelium could be seen in the anterior retina superior temporally and inferior nasally. Six months later the areas of RPE preservation were definitely smaller.

The photopic and scotopic electroretinograms were nonrecordable, and the final rod threshold was elevated by 3·25 log units. The Goldmann visual field with the IV-4 isoptre showed 3° centrally in each eye. A complete blood count, fluorescent treponemal antibody test, metabolic screen, and quantitative amino acids were normal.

CASE 4

This is a 65-year-old white female who noted night blindness by age 30 and stopped driving by age 45. The family history revealed a great-grandmother who went blind, a sister, now deceased, who had RP, and a first cousin once removed who is blind. There was no history of consanguinity in the pedigree.

On examination the patient's best corrected visual acuity was RE 20/200, LE 20/400, with a correction of RE +3·75 and LE +2·75. Slit-lamp examination revealed small posterior subcapsular cataracts in each eye. On indirect ophthalmoscopy the patient had a fundus of blond appearance, with vessel attenuation, optic atrophy, and scattered bone spicules and aggregations of pigment in the equator region. The blond-appearing fundus did not allow for the identification of the PPRPE pattern, and a fluorescein angiogram was obtained to look for the preservation of the RPE under the arterioles. Fig. 4 shows the posterior pole in which a small arteriole coursing temporally inferior to the macula shows the PPRPE pattern.

Visual physiological studies demonstrated a nonrecordable photopic and scotopic ERG with a 5·0 log unit elevation of the final rod threshold on dark adaptometry study. The patient had a 4° Goldmann visual field with a IV-4 isoptre in each eye.

CASE 5

This is a 15-year-old white boy who was noted to have night blindness and nystagmus at age 15 months.

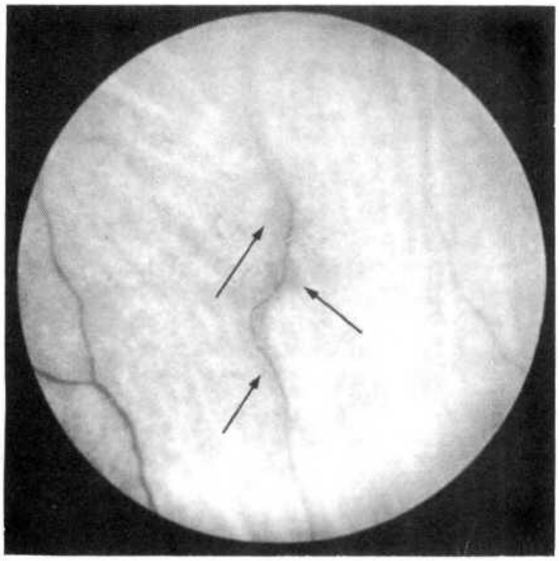

Fig. 5 *Fundus photograph of 15-year-old boy with PPRPE in all quadrants of each eye. Para-arteriole retinal pigment epithelium is preserved in anterior equator regions (arrows) despite extensive panretinal degeneration elsewhere.*

There is no family history of eye problems or consanguinity. Fundus examination at the time was reported as normal. Subsequent examinations at age 9 revealed mild pigmentary deposits in both eyes, and the diagnosis of retinitis pigmentosa was suspected.

On a recent examination at age 15 the patient had a visual acuity of RE 20/200, LE 20/400, with a correction of RE +3·00 +0·75×90, LE +2·50 +0·75×90. The patient had a rotary and jerk nystagmus. Slit-lamp examination revealed anterior and posterior subcapsular opacities in both eyes. Fundus examination revealed a blond fundus with generalised diffuse loss of the retinal pigment epithelium, optic nervehead drusen, and a few scattered pigment deposits in the posterior pole. Preserved para-arteriole retinal pigment epithelium could be seen in all quadrants of both eyes in the anterior equator region. Visual physiological testing demonstrated a nonrecordable ERG and a final rod threshold that was 4·15 log units elevated at 40 minutes. Goldmann visual fields with the IV-4 isoptre showed 7° showed central fields with temporal peripheral islands in each eye.

Discussion

It is important to review those features which support the view that the same disease process is taking place in these patients. In addition to the distinctive PPRPE pattern the patients had other similar appearances in the fundus. All 5 had fine round yellow retinal deposits in the posterior pole. The pigment was clumped in atypical irregular aggregations; and, while some vessels were coated with pigment, there was less generalised bone spicule formation[10] than is frequently seen in RP. The retinal blood vessels were not as attenuated as is frequently seen in advanced RP, and optic nervehead drusen were seen in 4 cases, with optic atrophy readily apparent in all cases.

While all these findings with the exception of the PPRPE pattern are seen in RP patients, they all occur less often in RP as a group. Optic nerve 'abnormalities' were noted only 65% of the time by Merin and Auerbach,[11] and in a recent survey of RP fundus photographs we found that 76% of RP patients have pink though not necessarily normal-appearing discs.[12] Other evidence supporting a single disease process is that all the patients were hypermetropic when RP patients as a group are myopic,[13] 4 of the 5 had optic nervehead drusen, and all 5 patients have pedigrees consistent with autosomal recessive inheritance.

The fact that these 5 cases showed focal preservation of the retinal pigment epithelium in areas adjacent to arterioles, despite a panretinal degenerative process, implies some type of positive interaction between the retinal pigment epithelium and the arteriole. In fact advanced disease is necessary to see the pattern of preservation.

Initially it might be assumed that an oxygenation effect from the arteriole helps to preserve the RPE. This does not appear to be likely, since the RPE does not derive its nutrition and oxygen from the retinal circulation. Furthermore any oxygenation effect is just as likely to come from the retinal capillary network as from the retinal arteriole.

If the effect was one of reducing light exposure by the shadow of the overlying vessel, then the same pattern would be expected under and adjacent to the veins. Examination of the choroidal vasculature on fundus photographs and fluorescein angiograms reveals no abnormalities of the choroidal circulation which would help to explain this phenomenon.

It is conceivable that a permeable factor is being released by the retinal arterioles which has a positive influence on the RP process, thereby temporarily retarding the degeneration locally in the areas of the retinal arteriole. If the primary aetiological process in these patients is in the bipolar layer, which receives nourishment from the retinal circulation, the retrograde degeneration[14] could cause loss of the receptors and RPE except in the proximity of arterioles.

Likewise transsynaptic degeneration would explain the optic atrophy seen in these patients. It is also possible that a permeable factor could reach the receptors of RPE directly.

Proving the existence of such a factor may be quite difficult, since the aetiology of the disease process is not known. However, understanding the role of the retinal arteriole in PPRPE would contribute significantly to determining the aetiology and pathogenesis of these patients' RP. The PPRPE pattern is not common; the frequency in our RP population has been less than 1%.

Preservation of posterior pole RPE is a common occurrence in RP; the central RPE will remain unchanged and functioning in many patients for a number of years. The reasons for the macular RPE being resistant to the disease are not known, but physiological differences between central and peripheral RPE are beginning to be reported[15] and eventually may clarify this mystery.

Retinitis pigmentosa is a nonspecific diagnosis, typically indicating a pigmentary retinopathy, nonrecordable or abnormal electroretinogram, and progressive visual field loss. However, because RP occurs in so many diseases and inheritance patterns, classification systems by aetiology or at least pathogenesis need to be developed. This will allow research efforts to be focused more effectively, and will aid the practitioner in more precisely diagnosing the various types of RP.

Dr Allan Kreiger, Dr William Stell, and Dr David Cogan reviewed the cases. Dr F. D. Ellis referred case 1. Jean Shimizu and Mada Barrett provided secretarial and editorial assistance.

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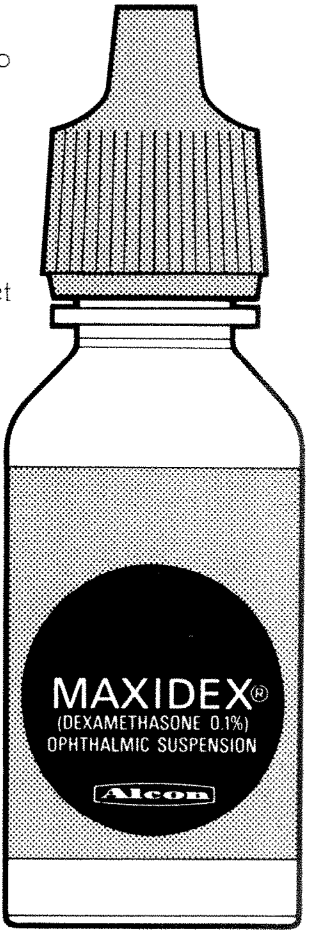

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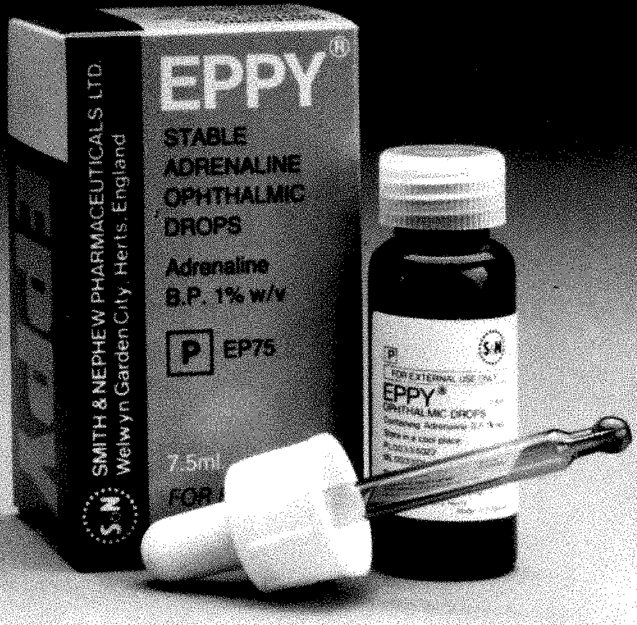

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British Journal of Ophthalmology, 1982, **66,** 31–34

The age variation of 'senile' cataract in various parts of the world

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SUMMARY As its name implies, senile cataract is age-related. A survey of 9 studies indicates to what extent the epidemiology of senile cataract can be represented by Gompertz plots. These are shown to be suitable separately for men and women and to enable one to distinguish between inborn and environmental influences. Further support is obtained for the view that myopia and cataract may be linked, and attention is drawn to the potentially noxious effect of (ultraviolet) light.

Nordmann[1] includes with senile cataracts all those without any known aetiology. Although some distinctions between different types are finely drawn,[2] Nordmann's approach has the merits of both simplicity and flexibility. That said, it may be of interest to collate statistics on the incidence of so-called senile cataract and to compare the data reported for different parts of the world.

Apart from the well-known cautionary remarks applied to all epidemiological studies, 2 additional caveats need to be made in the present context. Many definitions of (biological) age are on offer,[3–5] but in our case 2 special points arise. 'Senile' cataracts, like cardiovascular complications, may be part of a programme which limits the life span, furthers genetic novelty, and guards against overpopulation. Alternatively or additionally they may be due to cumulative effects of the environment. The relevant causes act all the time, but the repair processes find it progressively harder to deal with them.

Some of these points are relatively easy to assess. For example, other things being equal, a longer life stands a better chance of being subjected to environmental insults than does a short one. However, it is not found that ethnic groups with long life spans show a greater incidence of cataracts than those with short ones. The contrary holds in important examples like India. It is possible, though, that within an ethnic group an increase in life span will bring with it an increase in ophthalmological problems,[6] not to the exclusion of cataract.

If light, notably the ultraviolet,[7] is cataractogenic, then this effect would be pseudosenile: those living long would have received more of the noxious quanta than their younger compatriots, and would therefore be at greater risk.

If myopia has a bearing on cataract,[8] one would expect not only myopic nations to suffer from it more than do emmetropic or hypermetropic ones, but there would also be a cumulative, that is, pseudosenile, effect if the correlation is not primarily genetic but due, for example, to myopes accommodating less than do the rest.

Materials and methods

A risk (R) is expressible as a fraction, and it is therefore important to be clear about the numerator and denominator. Most published reports have defined the former as persons who have been diagnosed as having, or have had an operation for, cataract in at least one eye. Where the denominator is defined, for example, as the population attending eye departments and the relation between this and the total, that is, also healthy, population is undetermined, the computation of the risk fraction is unsatisfactory. So far as can be gathered from the authors of the studies here considered, the risks relate to the total population. In view of the high risk values, for example, in India, it is worth stressing that Chatterjee[9] carried out examinations on every tenth randomly selected person, a highly commendable approach. Others have given similar assurances.

All the data have been presented as Gompertz plots. Gompertz[10] used the exponential time scale for predicting mortality in Northampton. His approach has been modified by actuaries but von Bertalanffy[11] has given allometric examples which show the value

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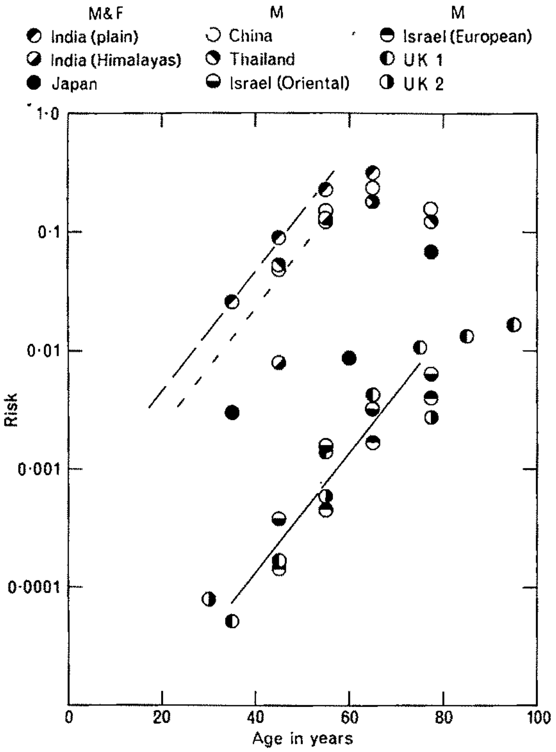

Fig. 1 *Gompertz plots for published senile cataract risks in various parts of the world. M=male.*

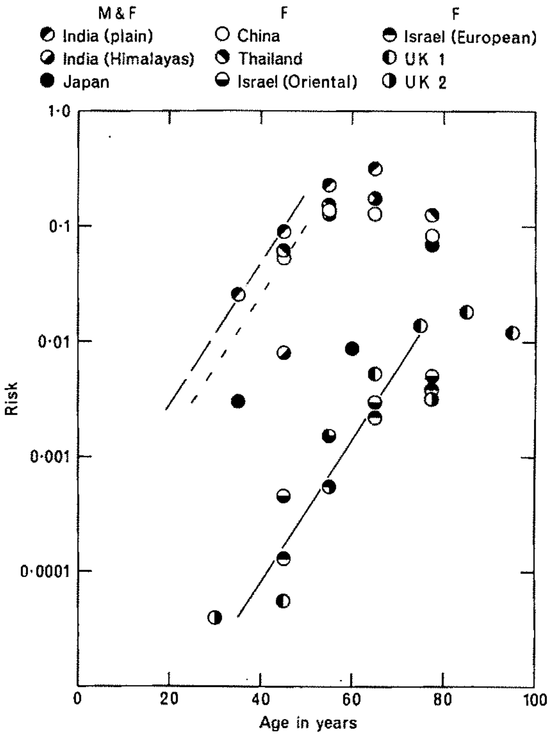

Fig. 2 *As for Fig. 1. F=female.*

and validity of the original expression. We shall consider its limitations below. The Gompertz equation is R=exp (+bt) where R is the risk, t the age in years, and b a constant which measures the rate of increase of the risk.

Wherever possible it is desirable to present men and women separately. There are indications[12] that in the West women are at a somewhat higher risk than are men, but that the reverse is true in the East.[13] The geographical difference may have one or more causes. In the Indian peninsula rural men are said to spend more time 'in the fields.' They may therefore be more exposed to light than are women. There are cultural differences between the importance attributed to women in different parts of the world, which may give rise to different thresholds of complaint about impaired vision. There are also hormonal effects,[14] and these may act at different ages in different parts of the world.

Results

Gompertz plots for the risk R are shown in Figs. 1 and 2. Where no sex separation is given the same data are plotted in both figures. Where there is a separation, the data for men are shown in Fig. 1, those for women in Fig. 2. The continuous straight line is the best fitting regression for the last 3 sets of data. In both Figures they provide a reasonable fit over 2 orders of magnitude of the risk. The slopes which are given by the above constant b do not differ significantly from each other.

The other dashed lines are merely parallel displacements of the above regressions. The long dashes serve to test whether the same value of b is applicable also to the high risk data. The shorter dashes are intended to illustrate an attribute of the Gompertz plot: a parallel displacement has a dual interpretation. In our case, looked on as a vertical (downward) shift, the short dashes betoken a risk reduction of 50%. But the same shift may be read in a horizontal direction as a delay of about 5 years.

Discussion

In spite of the apparent scatter of the data some broad conclusions emerge. It would seem that, except for the later part of the lifespan, the Gompertz plot presents a simple way of predicting the variation with age of the incidence of 'senile' cataract.[8] In the highest age groups the incidence is smaller than predicted, but this may be artefactual because of the progressive diminution in available numbers.[4] It is noteworthy that this discrepancy is manifest at both extremes of the risk range. The plots also show starkly that, for a given age group, the maximum groups are 400 times worse off than the minimal groups so far discovered. The challenge which this represents does not seem to me to have received the emphasis it deserves. It is to be noted that the 3 Mongol ethnic groups who tend to be myopic also seem to have large risk fractions, thus lending some support to the suggestion that lenticular mechanisms may provide a predisposing cause.[8]

It is evident that in its simple form the Gompertz equation fails to describe the above data in that it allows only for one line. A time invariant constant c formally describes genetic causes. Thus $R = \exp(bt + c)$ where c can assume different values. Now what about the environment, such as light, diet, etc?

If the constant b is given by a programme for aging —and the tentative conclusion from Figs. 1 and 2 does not render this unlikely—then environmental effects must manifest as changes in the slope of the course of the data. This can be revealed only at relatively early ages because of the failure of the Gompertz plot to account for risks of older age groups. The Indian data are very instructive from this point of view. Their authors expressly attribute the difference between the 2 altitudes to differences in ultraviolet exposure, the latter said to be more intense in the plains. However, anyone familiar with the villages in Kashmir will realise that this is not the only difference. The ethnic composition is different, with marked Mongol traits at high altitudes. But Mongol traits may include myopia, and it is noteworthy that even the youngest Himalayan group lies within Japanese limits. There is no doubt that there is a smart rise in risk soon afterwards. In other words, subject to confirmation, we have here the change in the b value advanced above as betokening an environmental difference. The Japanese results are too sparse to enable one to say whether a decrease in b is being observed.

Finally, a word of explanation is needed as to why no USA datum has been used. Van Heyningen[15] has indicated that the proportional number of operations in the USA is greater than in the United Kingdom. In so far as the ethnic combinations of the white populations may be comparable the reason for the factor may be sought in a greater sensitivity to pointers for the presence of cataracts on the parts of both the patient and the practitioner. Until this covertly cultural distinction can be ruled out, it will be prudent to omit the data from a transworld comparison. Nevertheless, an intracultural study of considerable interest[16] is clearly material to our considerations. These authors find, as van Heyningen[17] did before them, that cataracts extracted from outdoor workers tend to be more brunescent than those obtained from indoor workers. Van Heyningen had compared British and Pakistani samples, and the photic connection was not explicit. In the case of Zigman *et al.*[16] the samples are not all selected from within the United States but some allowance is made for geographical variation. Cross-cultural factors were more nearly controlled in a study by Hiller *et al.*,[18] who found in 2 US communities that differed significantly as regards solar irradiation durations that the ratio of cataracts to noncataractous disease controls was greater in the more exposed regions for persons above 65 years of age. While this does not formally rule out an inhibitory effect of light on the controls, the observation is consistent with other studies on the photogenesis of some types of cataract.

These highly revealing data need, however, amplifying before the risk[19] attributed to light, estimated (by the present writer) as a factor 5, can be fully validated. If myopia accounts for one order of magnitude,[8] then at least another order of magnitude remains to be accounted for as between the minimum and maximum incidence of 'senile' cataract shown in Figs. 1 and 2. It is hoped that the identification of possible causes may be facilitated by the above tentative analytic approach.

I thank Mrs C. S. Lawrence and Miss U. Farrell, Institute of Ophthalmology Library, for their help with literature searches.

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British Journal of Ophthalmology, 1982, **66**, 35–42

Prevalence and aetiology of cataract in Punjab

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SUMMARY Three districts in the Punjab plains were surveyed in 1976–7 for senile cataract and potential risk factors. The prevalence of senile cataract was 15·3% among 1269 persons examined who were aged 30 and older, and 4·3% for all ages. These figures confirmed previous reports of high prevalence. The prevalence was 1% for ages 30–49 and increased markedly in the sixth and seventh decades to 67% for ages 70 and older. Univariate age-adjusted analyses of selected socioeconomic, demographic, dietary, and other variables suggested that a higher prevalence was associated with being widowed, low education, use of rock salt in cooking, infrequent consumption of various protein foods (beans and lentils, milk, eggs, and curd), short height, and low weight. Multivariate analysis further suggested low total protein consumption as a risk factor that may account for as much as 40% of the excess prevalence of Punjab cataract over that in a US population study.

Cataract is a major cause of blindness worldwide, especially in the tropical belt, where most of the densely populated developing countries are located.[1] In India 40% of all blindness may be due to cataract[2]; 27 million persons are blind from cataract in one or both eyes,[1] and the prevalence of cataract is about 7%.[3] Most of these cataracts are unassociated with other eye diseases, and the resultant blindness is curable. Though hundreds of 'eye camps' and mobile eye clinics[4 5] are organised each year to serve the largely rural population, present levels of effort can restore vision to only a fraction of those blind and visually handicapped by cataract.

Surveys in different climatic zones in northern India have found cataract prevalence of 4–10%, with senile cataract appearing and steadily increasing after age 30 and with prevalence 13–36% among persons aged 30 and older.[6–10] Variations in prevalence may be related to different environmental factors, but differences in cataract definition and field survey methodology are likely to account for much of the variation. Nevertheless, the reported high prevalence significantly exceeds that reported in the United States[11] and other countries.

The aetiology of senile cataract remains obscure even though it is a common disease. In this study we verify a high prevalence area and attempt to identify factors related to the risk of developing senile cataract. In addition to general socioeconomic and demographic variables we also include nutrition,[12 13] fluoride[14] and other minerals in drinking water, genetics, and others, following suggestions in an earlier report.[9]

Subjects and methods

Census information was used to select 3 geographically identifiable districts in the green belt of the Punjab plains, of about 1500 population each, of which one-third were expected to be aged 30 or older; a section of Ludhiana city slums (fieldganj); a nearby village (Narangwal); and a more distant village in the region known for high fluoride content of household water (Bajakhana) (Fig. 1). Each district was mapped and its households and regular occupants enumerated and checked against the census lists.

Field work was done in 1976–7. Under the supervision of the principal investigator (AC) an ophthalmologist (ST) and an ophthalmic assistant visited each household during daylight hours and clement weather, and examined each member aged 30 or older who was present and willing to be examined. Absent members were examined when possible on repeated visits. Of 4762 persons enumerated 1529 (32%) were aged 30 or older and 83% (1269) of them were examined (Table 1). The response to examination was 76% for men and 91% for women; 52·6% of examinees were women.

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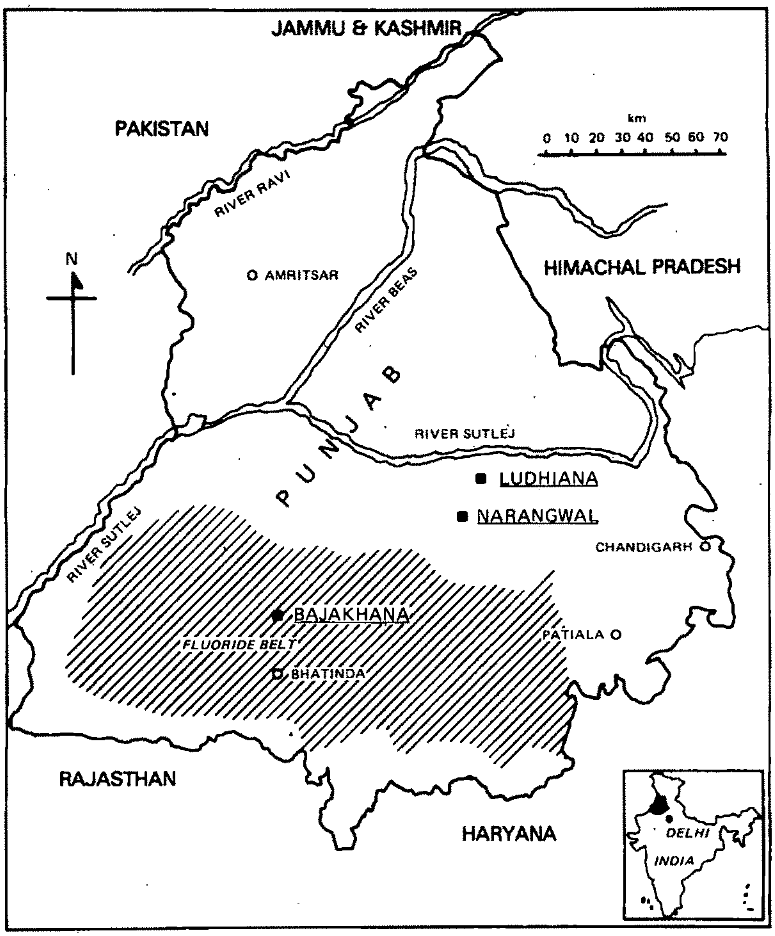

Fig. 1 *Study districts in Punjab: Fieldganj (Ludhiana), Narangwal, and Bajakhana.*

Examinations were performed according to a written protocol suitable for local field study conditions, and the results recorded on an examination form designed to facilitate coding for subsequent computer analysis. Responses to questionnaire items (Table 2) were recoded in appropriately defined categories. Visual acuity was tested with a Snellen illiterate E chart, held in the shade of a building so that it was not directly illuminated by sunlight, at a distance marked by a 6 metre rope. Acuity was recorded separately for each eye, the examinee occluding the other eye and taking care not to press on the eye. Acuity was tested with spectacles when available, and in all eyes with acuity less than 6/6 was further checked with plus and minus spherical lenses of power 1, 2, 3, and 4. Pinhole acuity was also tested for eyes with acuity less than 6/6. The best vision thus obtained was recorded.

Table 1 *Study census* and percentage examined, by age and sex*

	Male		*Female*		*Total*	
Age (yrs)	No. in census	% Examined	No. in census	% Examined	No. in census	% Examined
30–39	272	76	238	89	510	82
40–49	193	72	197	94	390	83
50–59	135	74	153	90	288	83
60–69	121	73	90	90	211	80
70–79	51	100	33	85	84	94
80+	24	83	22	95	46	89
Total	796	76	733	91	1529	83

*Number enumerated under age 30: 3233.

Lens examination was done in a dimly illuminated room in the examinee's house both with a uniocular loupe with oblique focal illumination and with distant direct ophthalmoscopy through an undilated pupil. Lens opacity location, form, and type were recorded according to the examination protocol. Opacities not of diabetic, traumatic, congenital, mixed, or other

Table 2 *Questionnaire items*

Age
Caste
Marital status
Economic status
Education
Usual occupation in last 10 years
Occupation location (indoors or out)
Cigarette smoking
Alcohol intoxication
'Usually urinate at night?'
'Sugar disease?'
Diet history: corn bread, wheat bread, beans and lentils, rice, meat, milk, eggs, curd, vegetables
Type of curd eaten
Use, type of salt
Water source
Weight
Height

type were designated senile type and further graded as to maturity.

Samples of drinking water were collected at random locations in each of the 3 districts and analysed for fluoride (F) by the colorimetric or visual comparison method at Patiala Medical College; for sodium (Na) and potassium (K) by flame photometry and calcium (Ca) by atomic absorption spectrophotometry, at the Department of Biochemistry, Christian Medical College Hospital, Ludhiana; and for magnesium (Mg by the versenate titration method at Punjab Agricultural University.

For prevalence and analysis of associations we used as a 'case' a person with aphakia not attributable by history or examination to specific causes, or an opacity of senile type accompanied by best visual acuity 6/18 or worse, in at least one eye. Prevalence is based on persons actually examined, with no adjustment for unexamined eligible persons. Association of single polychotomous variables with cataract was assessed by direct adjustment of prevalence to 10-year age groups of the total study population, and by the Mantel-Haenszel[15] significance test of 'average' relative odds comparing different levels of a variable. Note that the adjusted rates are valid for comparisons only within this study or in populations with similar age distribution.

The multiple logistic function,[16 17] $p=(1+e^{-y})^{-1}$ where $Y=a+\Sigma b_iX_i$, was used to examine multivariate association with senile cataract or aphakia. In this model p is the probability or risk of senile cataract or aphakia, the X_is are values of individual risk factors or variables (either discrete or continuous), and the b_is are coefficients to be estimated from the data. Positive coefficients indicate factors that increase risk. Maximum likelihood estimates of the coefficients were obtained by iteratively reweighted least squares.[17] Variables were selected for inclusion in the model from among those showing the strongest univariate associations, and were retained in the model if their contribution to association was significant and if they were not highly correlated with other variables in the model.

Results

Lens examination findings are summarised by location and type of opacity and gradation of senile cataract in Table 3. Opacities were found in 14% of the eyes of persons age 30 and older. Aphakia was unilateral in 30 persons and bilateral in 26 persons. Three-quarters of the senile cataracts were early immature (iris shadow present and some fundal detail visible by direct ophthalmoscopy).

Table 4 shows the prevalance of senile cataract accompanied by best visual acuity 6/18 or worse, or aphakia, by age and sex. Overall prevalence was 15·3% for ages 30 and older, and 4·3% for all ages assuming negligible occurrence under age 30. Bilateral senile cataract or aphakia occurred in 73%

Table 3 *Lens examination of persons age 30 and older*

	Number of eyes	*%*
Lens opacity location:		
No opacity, or aphakia	2161	85·1
Anterior cortex	5	0·2
Nucleus	151	6·0
Posterior cortex	52	2·1
Posterior subcapsular	8	0·3
Mixed	73	2·9
Other	67	2·6
Not done*	21	0·8
Total	2538	100·0
Lens opacity type:		
No opacity	2078	81·9
Aphakia†	83	3·3
Diabetic type	0	—
Traumatic	1	0·0
Congenital	11	0·4
Complicated cataract	4	0·2
Mixed	2	0·1
Unknown	3	0·1
Not done*	21	0·8
Other (including senile)	335	13·2
Total	2538	100·0
Senile cataract or aphakia:		
Aphakia (bilateral, 26 persons)	82	19·9
Senile cataract		
Early immature	248	60·0
Advanced immature	47	11·4
Mature	30	7·3
Hypermature	6	1·4
Total	413	100·0

*Includes 1 enucleation, 16 phthisis, 2 corneal leucoma, 2 'blind eyes.'
†Includes one aphakia due to trauma.

Table 4 *Prevalence of senile cataract* or aphakia, by age and sex*

Age (yr)	Sex	No. examined	Number with senile cataract or aphakia: One eye	Two eyes	One or two eyes	% One or two eyes
30–39	M	205	0	0	0	0·0
	F	214	0	1	1	0·5
	Total	419	0	1	1	0·2
40–49	M	138	1	2	3	2·2
	F	185	3	1	4	2·2
	Total	323	4	3	7	2·2
50–59	M	100	6	5	11	11·0
	F	138	14	10	24	17·4
	Total	238	20	15	35	14·7
60–69	M	87	8	24	32	36·8
	F	82	9	30	39	47·6
	Total	169	17	54	71	42·0
70–79	M	51	3	24	27	52·9
	F	28	3	14	17	60·7
	Total	79	6	38	44	55·7
80+	M	20	2	16	18	90·0
	F	21	3	15	18	85·7
	Total	41	5	31	36	87·8
Total	M	601	20	71	91	15·1
	F	668	32	71	103	15·4
	Total	1269	52	142	194	15·3

*With best visual acuity 6/18 or worse.

Table 5 *Distribution of frequency of use of food, according to response to interview, in percent*

Food	Number of times used per month: 0	1–5	8–20*	30–90†
Corn bread	57·4	9·7	3·2	29·7
Wheat bread	0·0	0·0	0·1	99·9
Beans and lentils	0·2	1·2	11·8	87·0
Rice	76·9	17·1	4·7	1·3
Meat	79·0	16·1	4·0	0·9
Milk	55·6	1·3	2·3	40·8
Eggs	82·9	7·4	6·3	3·4
Curd	54·8	5·0	9·2	31·0
Vegetables	12·8	0·0	0·7	86·5

*Two to 5 times per week.
†One to 3 times per day.

of the 194 cases. Prevalence increased steadily with age, with marked increases seen in the sixth and seventh decade. Age-adjusted prevalence was 13·7% for men and 16·9% for women aged 30 and older. This difference is of marginal significance ($p=0\cdot07$) and size of effect (combined relative odds=1·5). The lower rate of response to examination by men, together with the possibility that men away from home and working have less cataract than those at home, suggests the likelihood of a more definite sex difference in prevalence. Nevertheless, adjustment for sex was not done in subsequent analyses of association with single variables. Aphakia accounted for 24% of all eyes with cataract or aphakia in Table 4.

Table 5 shows the distribution of frequency of use of foods according to questionnaire response. Wheat bread, beans and lentils, and vegetables were each reported as eaten at least once a day by over 85% of the study population. Rice, eggs, and meat were each reported as never eaten by over 75% of the respondents. Analysis of association of food use with senile cataract was based on approximate tertiles of frequency of use.

Age-adjusted percentage cataract or aphakia is given in Table 6 for each level of selected questionnaire items, along with results of continuity-corrected Mantel-Haenszel significance tests of differences between levels. Age-adjusted prevalence for urban Fieldganj (18·5%) was higher than for either rural district, 13·8% and 13·6% ($p<0\cdot04$). Khatri and Arora caste members showed significantly higher prevalence than for the Jath caste ($p<0\cdot03$). Adjusted prevalence for widowed persons was higher than for married persons ($p=0\cdot001$). Prevalence decreased as economic status improved, and was significantly lower for high school graduates than for illiterates ($p<0\cdot03$). Usual occupation, location of occupation, cigarette smoking, and alcohol intoxication were applicable to men only, with no significant findings but with the suggestion of higher prevalence for indoor occupations, nonsmokers, and nondrinkers.

Affirmative response to 'Usually urinate at night?' and 'Sugar disease?', possibly indicative of diabetes, had higher prevalence of cataract or aphakia (although not significantly so) than negative response.

Among the dietary variables higher prevalence was associated with infrequent consumption of beans and lentils ($p<0\cdot005$), meat ($p<0\cdot06$), milk ($p<0\cdot04$), eggs ($p<0\cdot03$), and curd (or yoghourt) ($p<0\cdot02$). For curd made from buffalo milk, prevalence was higher for skim milk curd than for whole milk curd ($p=0\cdot05$); use of curd from cow's milk was rare. Prevalence was higher among persons using rock salt in cooking than among persons never using rock salt ($p<0\cdot01$).

Higher prevalence of cataract or aphakia was associated with short height ($p<0\cdot05$), with low weight ($p<0\cdot02$), and with low weight/height ratio ($p<0\cdot03$).

Analysis of mineral content of drinking water showed no differences among districts in mean calcium, potassium, and magnesium. The 2 rural districts have over 3 times (12 mEq/l) the sodium found in Fieldganj water. Average fluoride in Bajakhana (0·33 mEq/l, or 6·2 ppm) is markedly elevated as expected, 10 or more times that of either of the other districts.

Preliminary multivariate analyses, which included most of the variables showing significant or consistent

Table 6 *Age-adjusted percentage senile cataract or aphakia, by levels of single study variables*

	n†	%
District:		
Fieldganj	423	18·5
Narangwal	427	13·8
Bajakhana	419	13·6
*Fieldganj>Narangwal, Bajakhana p<0·04RO=1·78		
Caste:		
Khatri	80	19·9
Arora	296	18·3
Bania	52	16·8
Harijan	344	14·5
Ramagharia	61	14·1
Jath	393	13·1
Brahmin	21	8·3
Rajput	19	3·9
*Khatri, Arora>Jath p<0·03 RO=2·99, 1·86		
Marital status:		
Single	29	25·2
Widowed	138	22·2
Married	1099	13·9
*Widowed>Married p=0·001 RO=2·21		
Economic status:		
Poor	488	16·8
Low middle	667	14·9
Upper middle	114	11·8
Education:		
Illiterate	908	16·2
Can read	276	13·7
Highschool grad	85	4·2
*Illiterate>High school grad p<0·03 RO=7·46		
Usual occupation (men):		
Other	156	17·3
Farmer	102	15·6
Artisan	26	15·0
Business	124	11·0
Laborer	148	9·2
Professional	44	3·7
Occupation location (men):		
Indoor	288	17·1
Outdoor	267	12·5
Mixed	46	11·5
Cigarettes per day (men):		
None	533	15·2
<10	28	9·2
10–19	23	5·5
20+	17	10·4
—		
1+	68	11·4
Alcohol intoxication (men):		
Do not drink	262	17·2
Never/rarely	235	13·2
1/month	48	11·9
1/week	56	12·4
—		
Any drinking	339	12·9

	n	%
Usually urinate at night:		
Yes	36	32·7
No	1233	14·9
Sugar disease:		
Yes	9	21·6
No	1255	15·2
Corn bread, frequency per month:		
None	728	15·9
1–20	164	16·6
21–90	377	14·2
Wheat bread, frequency per month:		
8–30	22	11·3
31–60	648	14·6
61–90	599	15·9
Beans and lentils, frequency per month:		
0–20	165	21·1
21–30	1055	14·3
31–90	49	16·5
*0–20>21–30 p<0·005 RO=2·29		
Rice, frequency per month:		
None	976	15·1
1	112	17·0
2–30	181	14·3
Meat, frequency per month:		
None	1002	15·6
1–2	136	16·7
3–30	131	9·3
*None>3–30 p<0·06 RO=2·13		
Milk, frequency per month:		
None	706	16·7
1–20	46	19·2
21–90	517	13·1
—		
1+	563	13·6
*None>21–90 p<0·04 RO=1·57		
*None>1+ p<0·07 RO=1·48		
Eggs, frequency per month:		
None	1052	15·7
1–5	94	15·0
6–60	123	7·9
*None>6–60 p<0·03 RO=2·39		
Curd, frequency per month:		
None	696	16·1
1–20	180	18·0
21–90	393	12·1
—		
0–20	876	16·1
*None, 1–20>21–90 p<0·04 RO=1·71, 2·07		
*0–20>21–90 p<0·02 RO=1·81		

	n	%
Type of buffalo milk curd:		
No curd eaten	697	16·1
Home-made	505	13·0
Fortified	67	21·2
*Fortified>Home-made p=0·05 RO=2·26		
Vegetables, frequency per month:		
None	162	17·7
1–30	833	13·7
31–120	274	18·8
*31–120>1–30 p=0·01 RO=1·81		
Use of salt in cooking:		
Little	21	11·7
Average	1238	15·6
Much	10	0·0
Use of rock salt:		
Never used	934	13·8
Some use	335	18·9
*Some use>Never used p<0·01 RO=1·80		
Height, in cm:		
101–152	344	18·4
153–160	359	15·7
161–166	259	11·4
167–185	307	13·7
—		
101–160	703	17·3
161–185	566	12·6
*101–152>161–166, 167–185 p<0·05 RO=2·39, 1·87		
*101–160>161–185 p<0·01 RO=1·81		
Weight, in kg:		
23–45	401	18·7
46–52	293	15·2
53–60	269	12·4
61–99	306	11·7
—		
23–52	694	17·2
53–99	575	12·1
*23–45>53–60, 61–99 p<0·02 RO=2·01, 2·50		
*23–52>53–99 p<0·005 RO=1·88		
(Weight/Height)×1000:		
163–283	330	17·1
284–323	317	16·9
324–369	305	14·0
370–615	317	12·7
—		
163–323	647	16·9
324–615	622	13·1
*163–283, 284–323>370–615 p<0·07 RO=1·79, 1·84		
*163–323>324–615 p<0·03 RO=1·61		

*Significant differences; RO is relative odds by Mantel-Haenszel method.
†Number of persons at this level of the variable.

Table 7 *Multivariate risk function analysis, with risk factor coefficients ranked by t values*

Risk factor	*Coeff. B*	*Std. coeff.*†	*t*
Model 1:			
Age	0·1366	1·549	13·58
'Nutrition'	−0·0114	−0·341	−2·88
Married*	−0·7050	−0·228	−2·88
Weight	−0·0250	−0·283	−2·56
'Urinate at night'*	1·1305	0·185	2·31
High school graduate*	−1·5461	−0·385	−1·70
Constant	−7·9571		−9·25
Model 2:			
Age	0·1411	1·600	15·06
Constant	−9·4648		−16·68

*Yes=1, No=0.

†Standardised coefficient for variable X=B×SD (X), the contribution to change in log (p/(1-p)) for one standard deviation change in x.

univariate associations in Table 6, were used to select a subset of variables likely to contribute meaningfully to multivariate association with senile cataract or aphakia. A general nutrition variable was created as the total frequency of use of protein foods: beans, meat, milk, eggs, and curd. Table 7 shows the results of multiple logistic regression analysis of association of risk of senile cataract or aphakia with age, education (high school graduate), 'Frequently urinate at night?', weight, marital status (married), and 'nutrition' as defined above (model 1), and also with age alone (model 2). The number of expected and observed cases of senile cataract or aphakia is given by decile of risk in Table 8, indicating the adequacy of fit of the multiple logistic model to the data.

Table 8 *Distribution of senile cataract or aphakia by decile of risk from multivariate risk function*

Predicted decile of risk of senile cataract or aphakia	*Model 1 (6 variables)*			*Model 2 (age alone)*		
	No. expected	*No. observed*	*Maximum risk*	*No. expected*	*No. observed*	*Maximum risk*
1	0·3	1	0·004	0·7	0	0·007
2	0·8	0	0·007	1·0	0	0·011
3	1·2	0	0·011	1·5	1	0·016
4	1·9	1	0·019	2·5	1	0·022
5	3·3	0	0·034	4·2	1	0·043
6	5·9	2	0·060	6·8	7	0·083
7	11·3	12	0·126	12·4	14	0·154
8	23·9	31	0·259	25·2	31	0·270
9	47·9	56	0·534	46·6	55	0·498
10	97·6	91	0·998	93·1	84	0·989
	Sensitivity*		Specificity*	Sensitivity		Specificity
Upper decile of risk	0·47		0·97	0·43		0·96
Upper quintile of risk	0·76		0·90	0·72		0·89

*Sensitivity=a/(a+c), specificity=d/(b+d):

		Cataract	Noncataract
Risk Function	Top 10%	a	b
	Bottom 90%	c	d
	Total	a+c	b+d

Age alone was seen to be a good predictor of risk, with sensitivity 43%, and 72% for the upper decile and quintile of risk, respectively. The 6-variable model improves slightly the prediction ability, but with statistically significant contributions from all variables except possibly high school graduate, yielding corresponding sensitivities 47% and 76%. Risk decreases with increased 'nutrition', increased weight, for married persons, and for high school graduates. Risk increases with increasing age and for persons who frequently urinate at night. The relative odds (or relative 'risk') for one unit change in X_i, with the other Xs fixed, is e^{b_i}. One unit (year) increase in age is equivalent in relative risk to a decrease of 12 units in frequency of use of the foods in 'nutrition' and to 5·5 kg decrease in weight. The state of being married has relative risk equal to that of a decrease of 5 years of age. High school graduate status has relative risk equal to a decrease of 11 years of age. Similarly, frequent urination at night has relative risk equal to an increase of 8 years of age. Relative risk associated with an increase in age of 1, 5, 10, 20 years is 1·15, 1·98, 3·92, and 15·4, respectively.

Discussion

Prevalence of senile cataract in this study confirms the previously reported high rates for northern India. The age-adjusted prevalence comparable to the Framingham Eye Study is 43·3%, almost 3 times higher than observed in Framingham (Table 9). This difference is conservative, since our acuity criterion was more stringent, our method of examination (in field conditions, with loupe and ophthalmoscope through undilated pupils) might be expected to yield some false negatives, and lesser opacities detectable by slit-lamp were included in the Framingham study. The Punjab prevalence is consistent with Framingham prevalance about 14 years later in age. Average life expectancy in Punjab (about 65 years) is one of the highest in India and only 6 years less than in Framingham. The mortality rate for all ages is 7·9/1000 in Framingham and about 11·1/1000 in our rural-urban Punjab population. Age-specific mortality for Punjab and Framingham do not differ greatly for ages 40 and older (Table 10). These similarities, together with lack of reason or evidence for lower mortality with cataract in Punjab, suggests that the markedly higher prevalence in Punjab is due to factors other than differences in aging. There is at present no basis for assessing whether genetic difference is an important factor.

Table 9 *Prevalence of senile cataract or aphakia for Punjab and Framingham, by sex and Framingham age groups**

Age (yr)	*Sex*	*Punjab* %	*Framingham* %
52–64	M	26·2	4·3
	F	32·7	4·7
	Total	29·4	4·5
65–74	M	35·7	16·0
	F	52·6	19·3
	Total	43·3	18·0
75–85	M	79·3	40·9
	F	84·6	48·9
	Total	81·8	45·9
Total	M	36·2	13·2
	F	45·4	17·1
	Total	40·5	15·5
Total, age-sex adjusted to Framingham Eye Study population	43·3		

*Senile cataract definition includes best visual acuity 6/18 or worse (Punjab), 6/9 or worse (Framingham).

When making many statistical comparisons at a given significance level (such as p=0·05), as was done for univariate risk factors, one is likely to find about one in 20 comparisons 'significant' even when in fact there are no real associations. We find about 25 significant associations at that level out of over 130, suggesting that some of them are likely to be real. Independent studies are required to verify these associations.

Univariate association of senile cataract or aphakia with caste is not readily distinguishable from association with Fieldganj district, since 95% of Arora and Khatri castes and 1% of Jath caste were in Fieldganj. Similarly, all users of skim milk curd and rock salt were in Fieldganj. Thus, the elevated prevalence in Fieldganj may reflect the effect of rock salt in cooking, membership of the Khatri or Arora castes, lack of membership of the Jath caste, use of skim milk curd, use of water low in sodium, or some combination of these factors.

Table 10 *Age-specific annual mortality rates (per 1000) for Punjab and Framingham*

Age (yr)	*Punjab**	*Framingham†*
40–44	5·3	1·2
45–49	5·2	3·3
50–54	10·8	6·9
55–59	11·3	11·2
60–64	20·9	19·7
65–69	24·5	25·7
70+	96·8	82·2
All ages	11·1	7·9

*Sample Registration System, Punjab, 1976 (combined in proportion to study population: 2/3 rural, 1/3 urban).
†Massachusetts Department of Public Health, 1976.

Eight of the 9 positive responses to 'Sugar disease?' were in Fieldganj, and only one of the positive responses to 'Frequently urinate at night?' was in Bajakhana. Although these categories, especially the latter, are not definitively indicative of diabetes, the elevated prevalence for both categories is consistent with the known relationship between cataract and diabetes. Estimated prevalence of diabetes in this study for persons age 30 and older, based on positive response to these two questions, is 3% and is consistent with other reports on India.

Body weight, height, weight/height ratio, and frequency of use of protein foods, possible indicators of adequate nutrition, showed inverse association with cataract.

Multivariate analyses suggested that sex, economic status, use of rock salt, and Fieldganj district were unimportant in the prediction of risk of cataract when considered together with the factors in Table 7. Although age is, as expected, a strong predictor of risk, other factors also made statistically significant contributions. 'Nutrition' and weight are both significant, suggesting they singly are different or incomplete descriptions of nutritional status.

We find an association between low frequency of present use of protein foods and concurrent diagnosis of cataract. Although similar findings supported by data from nonexperimental studies in man are rare, anecdotal evidence such as given by Cass[18] implicates protein and other nutritional factors. If the present nutritional level of a study individual consistently reflects the relative level over the years, so that, for example, persons nutritionally lower than average today were lower than average 10 and 20 years ago, then the association may suggest a causal relationship.

This study suggests rather broadly that low protein intake (or possibly calorie intake) is related to early development of cataract. The design does not readily permit a finer breakdown of nutrition in terms of vitamins or aminoacids. Data available on Indian and US food and protein consumption are not fully comparable owing to differences in survey intent, detail, and methodology. Nevertheless, a rough nutritional comparison of Punjab and Framingham populations suggests that an increase in Punjab consumption of protein foods to the level of US consumption would, under the multiple logistic risk function model, reduce the expected Punjab prevalence of senile cataract for ages 30+ and 52–85 to 9·6% and 27·1%, respectively, a 37% reduction from the observed rates. Thus perhaps 40% of the excess of Punjab cataract prevalence over Framingham shown in Table

9 may be explained by current nutritional differences. The plausibility of a nutritional effect of this magnitude is enhanced by evidence that these 2 populations were even more nutritionally separated 10 to 20 years ago when a potential risk factor would logically have more causal impact on cataracts observed today. Still, the association of low protein consumption with increased development of cataract in man suggested here requires verification in more carefully designed studies. Especially helpful would be prospective studies or studies with stronger dietary components.

This study was supported in part by the National Society to Prevent Blindness, New York. Harold A. Kahn contributed significantly to development of the study concept and design and to early planning.

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British Journal of Ophthalmology, 1982, **66**, 43–45

Expulsive choroidal haemorrhage: an experimental study

H. ZAUBERMAN

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SUMMARY The closure of 2 or more vortex veins in rabbits' eyes results in a persistent rise in intraocular pressure. In these circumstances a small opening into the anterior chamber at the corneoscleral limbus resulted in an iris prolapse, while a larger limbal wound was immediately followed by a massive choroidal expulsive haemorrhage. It appears from this experimental study that a definite and persistent rise in intraocular pressure could be a sign of impaired venous outflow and that the occurrence of an iris prolapse after a small limbal opening into the anterior chamber should prompt us to examine the fundus of the eye and look for a choroidal complication. It is possible that the present set of experiments is relevant to the mechanism of expulsive haemorrhage in man.

Expulsive choroidal haemorrhage is a rare but dreaded complication of intraocular surgery. It appears that patients suffering from glaucoma, hypertension, diabetes, and high myopia have a higher chance of having this complication than normal patients.

The histopathology of human eyes removed after an expulsive choroidal haemorrhage has been described by Manschot.[1] He reported 6 cases which prior to surgery suffered from glaucoma. Five of the six cases showed a localised necrosis of one or more ciliary arteries. He postulated that an increase in the intraocular pressure causes arteriolar collapse and accelerates degeneration of the vessel wall, thus predisposing it to a rupture.

In one case[2] of spontaneous expulsive haemorrhage after a spontaneous rupture of a corneal ulcer the posterior ciliary artery appeared torn as it entered the suprachoroidal space.

From these reports it appears that a failure in the arterial circulation plus the sudden decompression of the eye, especially if it is glaucomatous, are the prime factors producing a massive choroidal haemorrhage. In the present experimental study I propose to investigate whether a failure in the venous choroidal outflow could be a factor in the development of an expulsive choroidal haemorrhage.

Materials and methods

Twelve albino rabbits were used in this study. The animals were anaesthetised with intravenous pentobarbitol 20 mg/kg and a 0·25 ml retrobulbar injection of Novocain (procaine) 2%.

In each rabbit the right eye was treated as follows: the conjunctiva was sectioned above the insertion of the lateral rectus muscle in 6 rabbits and above both insertions of the lateral and the internal recti muscles in the other 6. The sclera below the muscles was exposed by displacing the muscle fibres with a muscle hook. In 6 rabbits the 2 vortex veins underneath the upper and lower margins of this muscle were closed tightly with the aid of a 7/0 silk suture. In 3 rabbits 3 vortex veins were closed, 2 under the lateral rectus and one under the internal rectus muscle. In 3 rabbits 4 vortex veins were closed.

In every experiment the area of iris previously drained by the closed vortex vein was seen to become congested. When 2 or more vortex veins were occluded, petechiae appeared on the iris surface, and the choroid became congested in the affected area. In the rabbit the vortex veins drain not only the choroidal circulation but also the anterior segment of the eye, and this is why petechiae appear over the iris tissue when 2 or more vortex veins are occluded.

When 4 vortex veins were occluded, a mild haemorrhage was seen to appear on the iris near the angle. The choroid was seen to become quite congested, but no bleeding was detected in this tissue.

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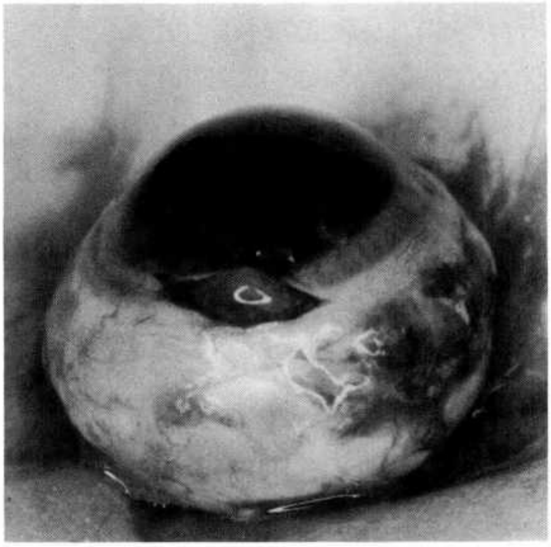

Fig. 1 *Small iris prolapse is seen after limbal opening into the anterior chamber.*

Prior to the retrobulbar injection of procaine and 5 minutes after the ligature of the veins the intraocular pressure was measured with the help of a Schiøtz tonometer in each of the 24 eyes under study.

Ten to 15 minutes after the closure of the veins the anterior chamber was entered through the corneoscleral limbus with the help of a sharp razor blade.

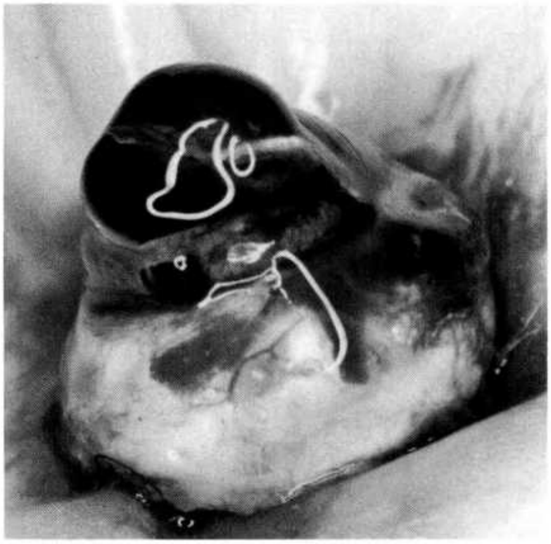

Fig. 2 *Expulsion of lens and vitreous resulting from choroidal haemorrhage.*

Then the corneal wound was enlarged along the limbus for a total length of 12 mm.

For the purposes of control the left eyes of the 12 rabbits underwent retrobulbar anaesthesia and measurement of the intraocular pressure before and after it. In each case a corneoscleral penetrating wound of 12 mm was induced as in the right eye.

Results

In the 12 eyes without vortex vein occlusion the intraocular pressure was of 16–18 mmHg before and after the retrobulbar injection of procaine. In the 6 eyes with occlusion of 2 vortex veins the intraocular pressure rose from 16–18 mmHg before the vein ligature to 22–24 mmHg 5 minutes after the ligature. In 2 of these 6 eyes the 3 mm limbal opening of the anterior chamber produced by the razor blade resulted in an instantaneous iris prolapse (Fig. 1), which could not be replaced by repeated trials. When this incision was enlarged, the whole upper iris prolapsed out of the eye. This was immediately followed by the spontaneous expulsion of the lens, a large amount of vitreous loss, and the development of a massive vitreous haemorrhage (Fig. 2). In the other 4 eyes with 2 vortex vein occlusions the corneal opening resulted in a moderate hyphaema but no other complications.

In the 6 eyes which underwent 3 vortex vein ligatures and in the 6 eyes which underwent 4 vein ligatures the intraocular pressure rose from 16–18 mmHg to 30–35 mmHg. In 3 eyes with 3 vein occlusions and in 5 with 4 vein occlusions an expulsive haemorrhage occurred, as described above.

In the 24 control fellow eyes the corneoscleral

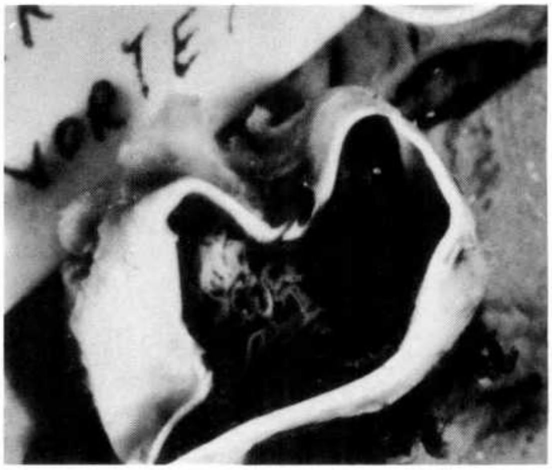

Fig 3 *Gross section of rabbit's eye: ciliary body and choroidal haemorrhagic detachment and retinal detachment.*

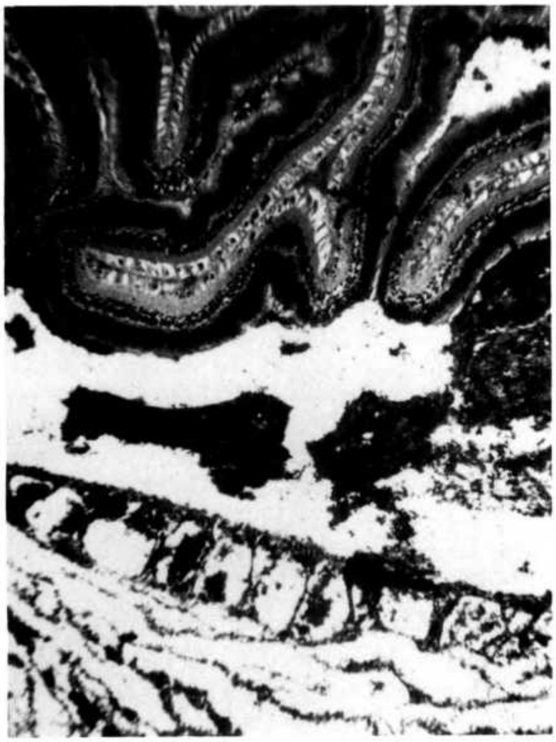

Fig. 4 *Perichoroidal haemorrhage. Retinal detachment. (× 10).*

opening into the anterior chamber was not followed by an iris prolapse or by a haemorrhage.

One eye affected with expulsive choroidal haemorrhage was enucleated and fixed in 10% formalin. Macroscopically this eye contained a haemorrhagic mass. The choroid and ciliary body were detached and the retina was detached and folded (Fig. 3).

Haematoxylin-eosin stained sections showed a severe choroidal and perichoroidal haemorrhage with a retinal detachment (Fig. 4) and a haemorrhage in the ciliary body.

Discussion

It appears from this study that it is possible to produce an experimental expulsive haemorrhage of the choroid by occluding partially or totally the venous outflow of an otherwise normal rabbit's eye.

In a previous study eyes removed after an expulsive choroidal haemorrhage were found to show necrotic changes in one or more posterior ciliary arteries. The rupture of the artery causing the haemorrhagic event was believed to be facilitated by the presence of previous degenerative changes in the vessel wall induced by an increased intraocular pressure, hypertension, diabetes, etc.[1] The possibility that a rupture in a degenerated artery was secondary to stasis in the choroidal venous flow was not then considered. However, Samuels[3] postulated that the invasion of fluid and blood into the perichoroidal space could result in traction on the arterial vessels and their rupture, and, if the bleeding is massive, the choroid may be ruptured, and the blood while flowing out of the globe carries along the intraocular contents. It is of interest that a blockage of venous outflow as demonstrated in the present study can reproduce so well the events of an expulsive choroidal haemorrhage. It is possible that a blockage in the venous outflow occurs occasionally during a surgical procedure in human eyes. A possible mechanism of venous closure could be pressure by the orbital contents on the vortex veins after an excessive amount of retrobulbar anaesthesia. Also, the accidental production of a retrobulbar haemorrhage could result in a compression of the vortex veins. Probably in those eyes in which the blood flow is already partially compromised, such as occurs in chronic glaucoma, systemic hypertension, and severe arteriosclerosis, the blockage of venous outflow is easier to obtain.

In the present set of experiments one important sign of venous flow occlusion has been a moderate to severe rise in intraocular pressure. This sign of venous stasis appears to be of importance. Indeed, a rise of the intraocular pressure as compared with the pressure prior to a retrobulbar injection could be a warning sign of venous outflow blockage. Furthermore, the presence of a spontaneous and recurrent iris prolapse after a small opening of the anterior chamber, such as occurred in this study, should make us aware of the possibility of venous stasis and lead us to examine the fundus of the eye for evidence of choroidal bleeding.

This study was supported in part by the Ignazius Sommers research fund.

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British Journal of Ophthalmology, 1982, **66**, 46–52

Visual disorders associated with cerebral palsy

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SUMMARY School children severely afflicted with cerebral palsy, but unselected in regard to their visual status, have been studied. Of 120 children examined only 24 (20%) had normal eyes or ocular adnexae. Squint was found in 52·5% of the children and significant refractive errors in 50%. There was also a high incidence of strabismic and anisometropic amblyopia (15%) and visual field defects (11%). A number of other ocular abnormalities were found, the majority of which were not amenable to any form of treatment. Early identification of treatable ocular defects and their treatment along conventional lines is emphasised. It is also important to identify untreatable defects that may have a bearing on the child's education. These children need all the help available, and visual function should be at its best. A diagnosis of cerebral palsy has usually been made by the time such a child reaches 18 months of age. In view of the high incidence of ocular defects a full ophthalmological assessment should be part of the routine assessment of the child.

Cerebral palsy consists of a group of conditions of different aetiologies but with distinctive clinical features. The motor abnormalities dominate the clinical picture and form the basis for the definition of cerebral palsy that is most widely quoted in the British literature. This is 'a persistent but not unchanging disorder of movement and posture, appearing in the early years of life, and due to a non-progressive disorder of the brain, the result of interference during its development.'[1] By general agreement specific degenerative and inherited conditions involving the central nervous system are excluded, although in any population of school children with cerebral palsy such conditions may be represented. It is customary to classify cerebral palsy on the basis of the type of motor abnormality and its topography.[2] Thus the majority of motor disorders are spastic, athetoid, ataxic, or atonic in that order of frequency, and the topography relates to the description of the limb or limbs involved—for example, monoplegia, diplegia, hemiplegia, tetraplegia, and quadriplegia. A child with spasticity involving both lower limbs would be described as having spastic diplegia. While the motor abnormalities are the most apparent clinically, there are commonly associated varying degrees of mental subnormality, emotional instability, and convulsive disorders. In addition sensory abnormalities, particularly deafness and visual disability, are common, and yet the latter still does not seem to merit the attention that it deserves. These multiple manifestations have led to the terms 'brain damage syndrome'[2] or 'perinatal encephalopathy'[3] being used, which perhaps are apter descriptions. However, the diagnosis of cerebral palsy is hallowed by tradition and will be retained here.

An estimate of the incidence in Scotland in 1964 was 750 per 1 million of the population.[4] It is possible that his number will have increased since then owing to improved perinatal care and greater numbers of affected children in better institutional care. So far as can be ascertained the figures are approximately similar for England and Wales. That cerebral palsy may be associated with an ocular abnormality has been known for over a century.[5] Within the last 2 decades several authors have drawn attention to this[6–10] and in particular the high incidence of squint[11] and refractive error.[12] Authors have also noted the risk of certain groups of children having their visual disabilities ignored or overlooked.[13] These include children with multisystem disease, mentally subnormal children, and those with neurological disorders. This study concerns the ophthalmological findings in a group of children afflicted with cerebral palsy.

Patients and methods

All the children that passed through a school for spastics within one 12-month period were examined.

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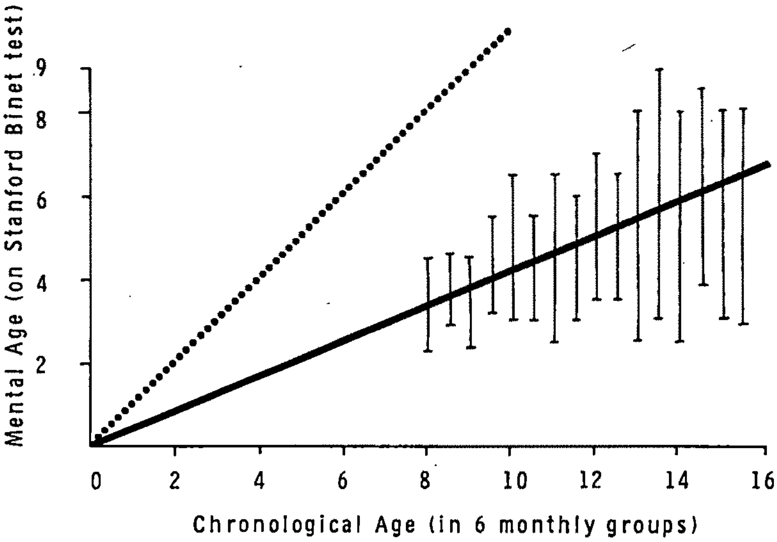

Fig. 1 *Mental versus chronological age in 120 children with cerebral palsy. The continuous line represents the average mental age of the children and the dotted line represents a population where chronological age matches the mental age. For further details see text.*

The criteria for selection to the school were that the child had a motor disability consistent with a diagnosis of cerebral palsy and was considered to be educationally severely subnormal, that is with an intelligence quotient (IQ) of between 30 and 50. Sensory handicaps were not considered in selection. There were 120 children between the ages of 6 and 16, of which 53 were female and 67 male. The majority (93%) were Caucasian.

Fig. 1 shows the mental ages plotted against chronological age in 6-monthly groups. The bars represent the limits of mental age within a particular chronological age group, the continuous line the mean of the mental ages, and the dotted line a population where the mental age is the same as the chronological age. It can be seen that the lowest mental age was just over 2 years and the highest 8·5 years.

All the examinations were performed at the school, in familiar surroundings, with either the child's nurse or teacher present. This is important for 2 reasons. Firstly, these children are easily frightened and require constant reassurance, and, secondly, those children who communicate with sign language need an 'interpreter' with them for the average ophthalmologist to be able to understand their responses. On principle it was decided that no child would be submitted to an examination under general anaesthetic unless the information likely to be gained would directly affect the child's medical care or education. This was not found to be necessary.

The examination consisted of lid position and movements, ocular movements, cover test, visual acuity, visual fields, colour matching, and a cycloplegic refraction and fundus examination some 40 minutes after the instillation of 1% cyclopentolate. No adverse reactions to this drug were noted, though an increased incidence of side effects in such children has been reported.[14]

The visual acuity was measured either with Sheridan-Gardiner single optotypes or with the Catford drums. It is appreciated that comparison of acuities obtained by the 2 methods is difficult and that acuity as measured was subject to many variables, not least being the child's mood and ability or will to concentrate. For this reason the results are not reported, although the information gained was of importance for schooling. Visual fields were assessed with the Juler projection scotometer. This instrument was invaluable with children who could not or would not fix on a target. Positive responses were noted by pointing, head turning, or in the case of uncooperative children by visually directed responses. The end wall of a room was used as a screen, this containing approximately the central 40° of field at the distance used. Colour matching was performed with pieces of felt. The colours used were red, green, dark orange, light green, light orange, light blue, yellow, dark blue, and dark green arranged in that order on a circular piece of cardboard. The colours used were dictated by commercial availability rather than scientific selection. For educational purposes this was considered adequate. The fundus was examined with the indirect ophthalmoscope.

Results

Table 1 summarises the types of cerebral palsy seen, classified in the usual manner, and Table 2 lists the

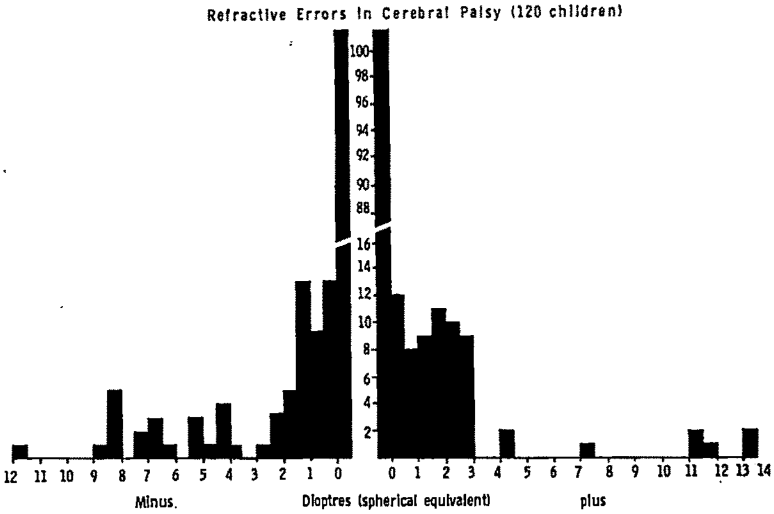

Fig. 2 *Histogram showing the range of refractive errors seen in cerebral palsy.*

aetiologies where known. In many cases there were a combination of circumstances that could have led to brain damage. In such cases the first event has been taken to be the causative factor. There are several strong correlations. Thus prematurity was associated only with spasticity, either diplegia, tetraplegia, or quadriplegia. Rhesus incompatibility and subsequent kernicterus were associated only with athetosis, though 50% of athetoids had suffered from a hypoxic episode during or soon after birth. Of the hemiplegics 42% acquired their lesions as a result of an incident after the perinatal period (road traffic accident, cerebral haemorrhage, meningitis). Infection in utero was presumed to be the cause of the lesions in 11 children, 6 with proved rubella and 2 with cytomegalovirus infection. The other 3 were thought to have suffered from intrauterine rubella, but without supporting laboratory confirmation.

The range of refractive errors found is shown in Fig. 2, plotted in spherical equivalents (sphere+½ cylinder). Age has not been taken into account, since there is evidence to suggest that refractive errors in this group of people do not follow the normal trend of change with age,[15] particularly hypermetropes. It has been postulated that this is related to a failure of maturation of the central nervous system, though skeletal growth is usually normal, albeit modified by the muscle disorders. The use of spherical equivalents permits ease of display but hides a number of significant astigmatic refractive errors. There were 16 such children with astigmatic errors between +1·5 and −1·5 dioptres spherical equivalent. Of the myopes exceeding −4 dioptres 6 had been premature, of which 3 had cicatricial changes of retinopathy of prematurity. There was a small number of aphakic eyes.

The incidence of refractive error found within the major groups of cerebral palsy is shown in Table 3. It can be seen that spastic diplegia in particular carries with it a high risk of refractive error and athetoid cerebral palsy the least risk. Of the children who acquired their cerebral palsy after the perinatal period half had significant refractive errors. The overall incidence of refractive error in this series was exactly

Table 1 *Incidence of type of cerebral palsy in the series, classified by motor abnormality*

	Number	*Percentage*
Spastic diplegia	38	31·6
Spastic tetraplegia/quadriplegia	36	30
Spastic hemiplegia	12	10
Athetoid	8	6·7
Athetoid with spasticity	11	9·2
Ataxic	7	5·8
Ataxic with spasticity	3	2·5
Others	5	4·2
Totals	120	100

Table 2 *Aetiology of cerebral palsy in 120 children*

	Number	*Percentage*
Asphyxia or birth injury	37	30·8
Prematurity	24	20
Rhesus incompatibility	5	4·2
Presumed placental insufficiency	9	7·5
Infection in utero	11	9·2
Familial	3	2·5
Unknown (with adequate history)	11	9·2
Postnatal insult (mixed aetiologies)	12	10
Inadequate information	8	6·6
Totals	120	100

Table 3 *Incidence of refractive error greater than −1 to +1·5 dioptres in the major groups of cerebral palsy*

Type	*Number of patients*	*Percentage abnormal*
Spastic diplegia	38	68
Spastic tetraplegia/quadriplegia	36	52·8
Spastic hemiplegia	12	41·7
Athetoid	8	37·5
Athetoid plus spasticity	11	27·2
Ataxic	7	42·8
Ataxic plus spasticity	3	0

50%, higher than in other series, and is perhaps a reflection of the severity of the cerebral palsy. Twenty-eight pairs of spectacles were prescribed, in addition to those already being worn by 14 children. Patient acceptance was high.

The incidence of squint found in this group of children is given in Table 4. Among the concomitant squints the convergence:divergence ratio was 2·3:1 (usually 8–10:1 in a 'normal' squinting population), and is in line with other workers' findings. Eleven of the concomitant squints had obvious abnormalities of the eye itself (disc abnormalities, retinopathy of prematurity, cataract, anterior chamber cleavage syndrome, and Leber's amaurosis), leaving 32 in which, other than refractive error, no obvious ocular lesions were present. There were 18 children with incomitant squints, of which two had Duane's syndrome, both associated with spasticity. Among the 16 children with cranial nerve palsies were 5 with 3rd nerve palsy, 3 with 4th nerve palsy and 8 with 6th nerve palsy. The highest incidence was seen in children with spastic hemiplegia.

Table 4 *Incidence of concomitant and incomitant squint in different types of cerebral palsy*

Type of cerebral palsy	*Number*	*Concomitant squint*		*Paralytic squint*		*Duane's syndrome*	
		Number	*Percentage*	*Number*	*Percentage*	*Number*	*Percentage*
Spastic diplegia	38	18	47·4	4	10·5	1	2·6
Spastic tetraplegia/quadriplegia	36	12	33·3	6	16·7	1	2·8
Spastic hemiplegia	12	3	25·0	3	25	—	—
Athetoid	8	2	25·0	—	—	—	—
Athetoid with spasticity	11	2	18·2	2	18·2	—	—
Ataxic	7	2	28·6	1	14·3	—	—
Ataxic with spasticity	3	1	33·3	—	—	—	—
Others	5	3	60·0	—	—	—	—

Table 5 *Nystagmus, gaze palsy, and ptosis in 120 children with cerebral palsy*

Type of cerebral palsy	*Number*	*Nystagmus*	*Gaze palsy*	*Ptosis*
Spastic diplegia	38	7	1	2
Spastic tetra/ quadriplegia	36	6	2	0
Spastic hemiplegia	12	2	1	0
Athetosis with spasticity	11	0	1	0
Ataxia	7	4	0	1

At this stage it is pertinent to comment on the number of children with amblyopic eyes. In the context of this study amblyopia was presumed to exist when there was a difference of 3 grades on acuity testing between the 2 eyes, or a reluctance to have one eye covered, with correction worn. There had to be a predisposing cause (anisometropia, squint, or ptosis) and an absence of obvious retinal or other lesion. There were 18 children with amblyopic eyes, an incidence of 15%. This could well be an underestimate because of the difficulty of assessing visual acuity in these children.

Table 5 shows the numbers of children with nystagmus, gaze palsy, and ptosis, an incidence of 15·8%, 4·2%, and 2·5% respectively. Nystagmus was found only in the ataxic and spastic types of cerebral palsy. Jerky eye movements, not amounting to true nystagmus, were seen in 3 children with spasticity. Eight of the 19 children had searching or pendular nystagmus associated with obvious ocular lesions, with a very marked latent nystagmus superimposed in 4. A further 3 children with pure latent nystagmus were seen, associated in each case with a convergent squint. Of those patients with central nystagmus 3 had upbeat nystagmus and 5 horizontal nystagmus. All of the former and 1 of the latter had pure ataxic

Table 6 *Abnormalities of field in 120 children with cerebral palsy*

Type of cerebral palsy	*Number*	*Field defect*	
		Hemianopia, number	*Constriction, number*
Spastic diplegia	38	2	3
Spastic tetraplegia/ quadriplegia	36	3	4
Spastic hemiplegia	12	1	—

Table 7 *Abnormalities of the eye in 120 children with cerebral palsy*

Ocular abnormality	*Type*				*Total*
	Spastic diplegia	*Spastic tetra/ quadriplegia*	*Spastic hemiplegia*	*Other*	
Microphthalmos	2	2	—	1	5
Buphthalmos	1	—	—	—	1
Corneal opacity	—	—	1	2	3
Cataract	2	1	—	—	3
Heterochromia iridis	1	2	—	—	3
Uveal coloboma	1	1	—	1	3
Pigmentary retinopathy	2	1	—	—	3
Retrolental fibroplasia	1	1	1	—	3
Optic atrophy	2	8	2	—	12
Optic hypoplasia	2	1	—	—	3

cerebral palsy. The lesions in these children are presumed to be in the cerebellum. No nystagmus was seen in any child with an athetoid component to his or her disorder. Gaze palsies were seen in 5 patients. Interestingly, 4 had abnormalities of head size, 3 being microcephalic and one hydrocephalic, secondary to neonatal meningitis. Only one gaze palsy was horizontal, the rest being elevator palsies. Ptosis, other than as part of a 3rd nerve palsy, was seen in 3 children, 1 of whom had an associated superior rectus weakness and an amblyopic eye.

Table 6 shows the field defects found in the 120 children examined. They were found only in children with spastic cerebral palsy. It was not found to be particularly difficult to assess field, though there can be no doubt that the method used underestimates the number of individuals affected, particularly with constricted field. There were 13 children (11%) with gross defects. Only 1 hemianopia was found in the hemiplegia children. Of the children with constricted fields, all but 1 had optic disc or retinal abnormalities. It is noteworthy that field defects were not detected in 8 children with optic atrophy or optic disc hypoplasia. This is a reflection of the difficulty of examining the field in any detail in children whose ability or desire to co-operate may be extremely limited. If one assumes that all these children had defects of field, then a truer incidence overall would be nearer to 17%.

The types of abnormality of the globes found in these children are shown in Table 7. Microphthalmos was seen in association with spasticity in 4 patients and in 1 child with atonic cerebral palsy. In 1 case it was associated with uveal coloboma, central anterior synechiae, shallow anterior chambers, disc hypoplasia, and absence of the septum pellucidum. Rubella was the causative factor in 2 of the children with microphthalmos, as it was in the 1 child with buphthalmos. Two other patients had corneal abnormalities. One had recurrent herpes simplex keratitis, and the other had nonsyphilitic interstitial keratitis associated with neurosensory deafness. Uveal coloboma was seen in 3 cases, an incidence of 2·5%, which compares with other series.[9] The association of uveal coloboma and mental disorder is well recognised.[16] A surprising finding was 3 cases of heterochromia of the irides. One child had facial hemihypertrophy on the more pigmented side, but there were no other signs of conditions known to be associated with congenital or acquired heterochromia. This abnormality was seen only in spastic children, as was congenital cataract.

So far as the retina was concerned, there were 3 children with cicatricial retinopathy of prematurity. In none had the diagnosis been made before this examination. There were 3 other children with myopia associated with prematurity. None had obvious retinal changes of retinopathy of prematurity, but it was not possible to submit these children to scleral depression to examine the extreme retinal periphery. Rubella retinopathy was seen in 2 children and what was thought on clinical grounds to be Leber's amaurosis in 1 child. Electrical tests of retinal function had not been performed.

Optic atrophy was seen in 10% of the children. Difficulties may be experienced in deciding clinically whether a disc is pale or atrophic, particularly when co-operation is limited. If doubt existed, the disc was classed as normal, so 10% may be an underestimate. Disc hypoplasia, seen in 3 children, was diagnosed when there was no doubt the diagnosis and not just for small discs. With 1 exception disc abnormalities were associated only with spasticity. The incidence of colour defects was 8% of the males, no more than would be expected in the general population.

In this series only 24 children (20%) had normal eyes on the examination described. Spasticity carried with it the highest chance of ocular abnormality, ranging from 91% in hemiplegia to 78% in quadriplegia. Athetoid and ataxic children were least likely to have ocular disorders, this incidence varying between 62% and 72% depending on whether spasticity was absent or present.

Discussion

Ocular abnormalities are very common in children with cerebral palsy. In any group of such children there will be a small number with specific syndromes or diseases of which an ocular disorder forms a part, for example, congenital rubella. However, the majority do not have specific and recognisable diseases and fall into a group of brain damaged children. Spastic children are more likely to have ocular defects than athetoid and ataxic children. The pathology in spastic children is more extensive and diffuse, with periventricular haemorrhage, subcortical haemorrhage, and cortical atrophy. In athetoid children it is centred on, although not confined to, the basal ganglia and in ataxic children on the cerebellum. This perhaps explains why spastic children have a higher incidence of ocular defects. The results of visual acuity testing have not been reported for reasons already stated. Douglas[9] has reported on the range of visual acuities found in such children and commented on the difficulties of assessment. Refractive errors and squint form by far the largest group of abnormalities. Fantl and Perlstein[12] have shown that myopia predominates in the spastic group. This is explained partly by the high numbers of premature children in this group. If those myopes associated with prematurity are excluded, there is a bias towards hypermetropia in this series, confirming the findings of other workers.[17] In the dystonic cerebral palsies hypermetropia predominates. This has been explained as a failure of maturation of the visual system related to neonatal hypoxia.[15] It does seem clear that the normal changes with age that occur in hypermetropia do not occur in cerebral palsied children. However, for this to happen it has been stated that the injury has to occur during the perinatal period, otherwise the incidence of refractive error approaches that of a normal population. In the, admittedly small, number of children in this series who acquired their cerebral palsy at least 21 days after birth, 50% had refractive errors, and this is contrary to previous findings.

Squint was found in 52·5% of the children. This compares with previous reported incidences of between 25%[18] and 60%.[7] There was a relatively low incidence of paralytic squint compared with Smith's series.[19] In his series the average age of the children was much lower, and this at least in part is a reflection of the tendency for concomitance to develop with age.

The relative infrequency of Duane's syndrome in cerebral palsy has been the subject of comment.[9] Many authors have considered the treatment of squint unrewarding because of the low rate of success as assessed along conventional lines and the high incidence of consecutive squint following surgery, due in part at least to central obstacles to fusion. However, Hiles and colleagues[20] treated 234 children with cerebral palsy and squint along conventional lines. They considered that 90% of their children achieved satisfactory ocular alignment during an average follow-up of just over 4 years. More importantly, they observed 80 children with amblyopic eyes and achieved 'good' results with conventional treatment. There is some evidence that visuospatial difficulties encountered in such children are exaggerated by the presence of squint.[21] It thus seems reasonable that every attempt should be made to treat the squint as if the child was otherwise normal. Even the purely cosmetic aspects assume importance, both for parent and patient, though squint surgery may have to be balanced against submitting a child to yet another surgical procedure.

The treatment of amblyopia is also important and the identification at an early age of defects likely to lead to it. The very nature of the child's underlying disability will render him or her accident prone, particularly when the shelter of school is left behind. Although no figures can be found, it must remain a possibility. Every effort should be made where possible to ensure that both eyes have useful vision.

Field defects do not seem to have merited the attention that they deserve. Harcourt[22] commented on the importance of identifying field defects, and in the children in this series the teachers in particular felt that substantial field defects were a special handicap and that the children did not adapt particularly well to them. Only 1 hemiplegic child was found to have a hemianopia, contrary to at least 1 previous report, which puts the incidence as high as 25% in cases of infantile hemiplegia.[23] It is important to identify field defects for 3 reasons. Firstly, failure to recognise a field defect, particularly hemianopia, may mislead an examiner performing psychological assessments. The fact that a child does badly when scanning from left to right might be put down to his mental subnormality rather than a right homonymous hemianopia. There may also be reading problems if the child learns to read. Secondly, if that eye is amblyopic, problems could arise when occlusion is planned. Thirdly, teachers aware of field defects may modify the way they physically approach a child, particularly if he or she is hemianopic.

There was 1 spastic child with septo-optic dysplasia. This boy also had an anterior chamber cleavage syndrome, an association not previously described, so far as can be ascertained from the literature.

Defects of the globe are, with the exception of cataract and glaucoma, untreatable. However, their recognition may aid in identifying the aetiology of cerebral palsy in that particular case. The rather high incidence of ocular defects found in this series in comparison with other workers' findings, is probably a reflection of the severity of the cerebral palsy. Evidence suggests that the degree of ocular abnormality increases with the degree of mental subnormality.

Conclusion

Visual disabilities in children with cerebral palsy are common. Errors of refraction, squint, amblyopia, and field defects are seen in a high percentage of these children. When possible it is important to identify and treat these defects along conventional lines. The education of these children relies heavily on visual stimulation, particularly those with sensory deafness. The teachers particularly need to know the visual acuity, defects of visual field, and colour matching ability. Children with multiple handicaps require as much help as possible, and this should include thorough ophthalmological assessment and care. The diagnosis of cerebral palsy has usually been made by the time such a child reaches 12 months of age, and rarely after 18 months. It is at this time that the child should have his or her initial ophthalmological assessment.

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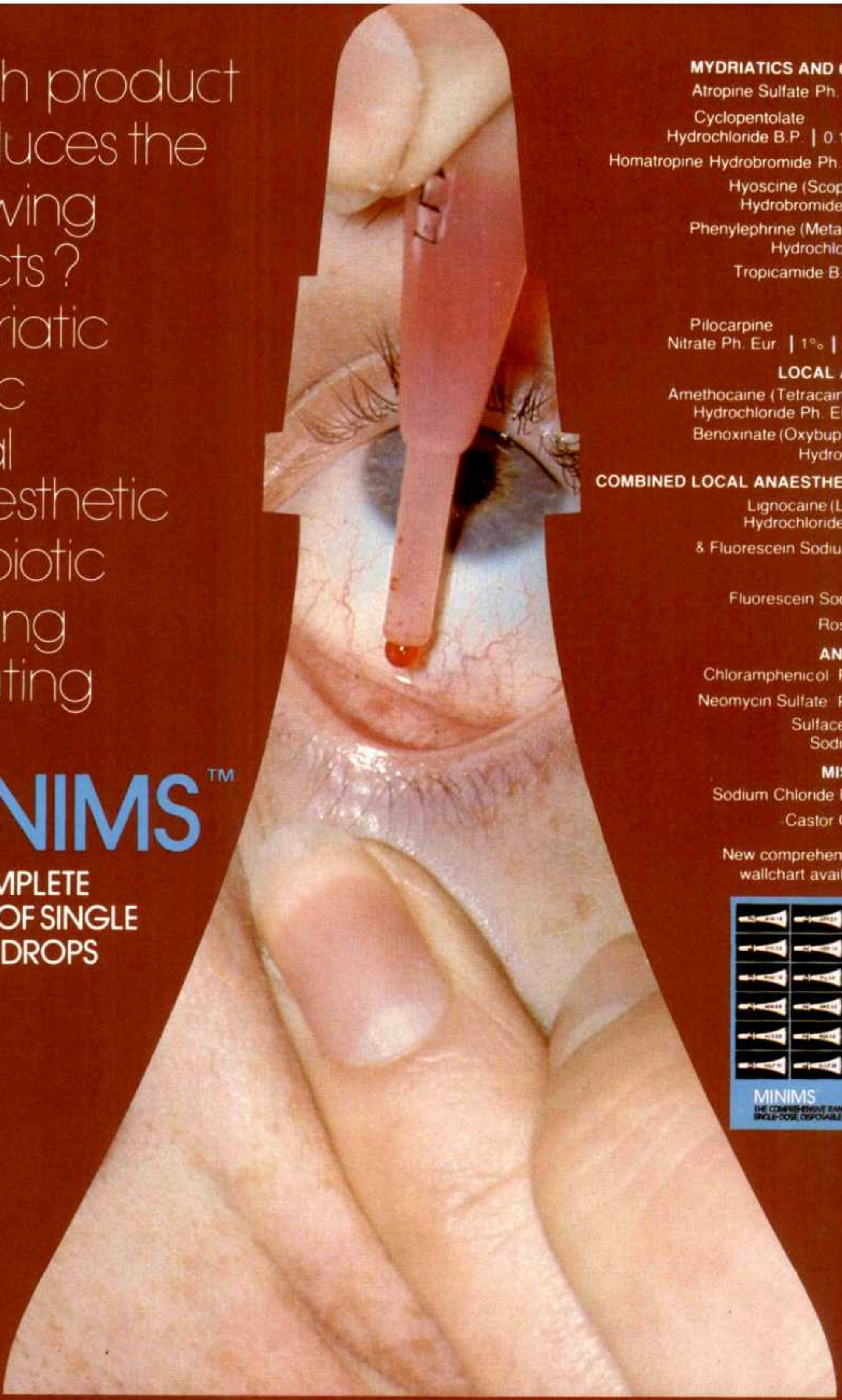

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Provided that the intra-ocular pressure is maintained at satisfactory levels many patients can then be placed on once-a-day therapy. However, because of naturally occurring diurnal variations in intra-ocular pressure, satisfactory response is best determined by measuring the intra-ocular pressure at different times during the day.

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When only a single antiglaucoma agent is being used, continue the agent and add one drop of 0.25% 'Timoptol' in each affected eye twice a day. On the following day, discontinue the previous agent completely, and continue with 'Timoptol'. If a higher dosage of 'Timoptol' is required, substitute one drop of 0.5% solution in each affected eye twice a day.

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Intraocular lens power calculation for emmetropia: a clinical study

JEFFREY S. HILLMAN

From the St James's University Hospital, Leeds

SUMMARY A series of 50 eyes received an intraocular lens (IOL) of power calculated for emmetropia from data of axial length, corneal curvature, and postoperative anterior chamber depth by R. D. Binkhorst's formulae. The postoperative refraction results were compared with those of 100 control eyes which received +19 D standard power IOLs without calculation. The calculated group had postoperative refractions which were closer to emmetropia, and the difference was of statistical significance, with 92% within the ±1 D range and 98% within the ±2 D range from emmetropia. The calculated predictions of postoperative refraction were of a useful level of accuracy. Consideration of the sources of error indicates that there is no justification for the use of IOLs in power steps of less than 1 D. The calculation of IOL power allows the surgeon to control the postoperative refraction and avoid unwanted ametropia.

The intraocular lens (IOL) is being used in the surgical management of cataract by an increasing number of British surgeons because of the high quality of resulting vision without demands on the patient. The quality of postoperative vision depends to a degree on the postoperative refractive error. Postoperative astigmatism may be controlled by careful surgical technique with particular attention to suture placement and tension. The residual spherical error is a function of the basic refractive power of the aphakic eye and the power of the IOL which is implanted. The use of IOLs in a standard power gives a satisfactory postoperative refraction in a large percentage of cases, but there remain a number of eyes with unplanned postoperative ametropia. The use of IOLs of different powers selected after calculations made preoperatively from data of ocular dimensions offers a way of controlling the postoperative refraction.

A previous study[1] showed that the cautious use of IOLs in a narrow range of powers around the standard power does not significantly influence postoperative ametropia compared with the use of IOLs of standard power. It was suggested that this is because ametropia occurs in eyes with abnormal ocular dimensions which need IOLs of more extreme powers. This paper reports a prospective study investigating the degree of control over postoperative refraction which can be obtained by the use of IOLs in a wide range of powers as calculated to give emmetropia.

Material and methods

The study was conducted on 150 eyes undergoing cataract extraction with implantation of a Binkhorst iris-clip IOL. The control population of 100 eyes received an IOL of standard +19 D power. Forty-two patients were male, 52 were female, and 6 had bilateral surgery. Their mean age (±SD) was 67·4± 14·5 years, and the range of preoperative refractions of the eyes is shown in Fig. 1.

The study population consisted of 50 eyes in 18 males and 32 females which received an IOL of power the nearest whole dioptre to that calculated to give emmetropia. They were of mean age (±SD) 71·4±7·3 years and the range of preoperative refractions shown in Fig. 1 indicates that the group is comparable with the control group.

The calculation of IOL power was based on data of corneal curvature, axial length, and a figure for the postoperative anterior chamber depth. Corneal radius of curvature was taken as the average of measurements in 2 meridia with a Haag-Streit keratometer. Axial length was measured with a Kretz 7200 MA ophthalmic A-scan ultrasound instrument with a 10 MHz transducer. The probe was coupled to

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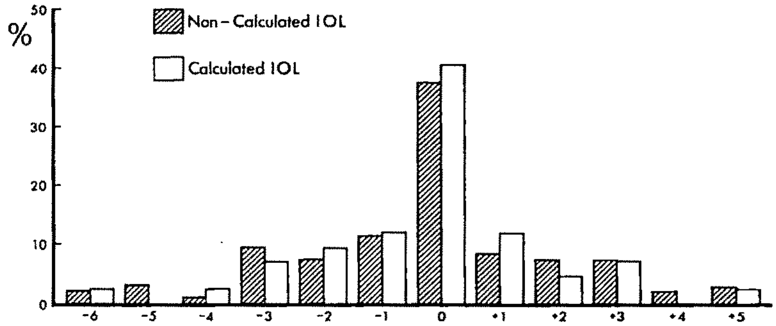

Fig. 1 *The preoperative refractions (spherical equivalent) for the control and calculated IOL groups.*

the anaesthetised eye by 5% methylcellulose solution in a contact lens water bath. Measurements were obtained from Polaroid photographs taken when axial alignment of the ultrasound beam was indicated by high echo peaks from the cornea, both surfaces of the lens, and the vitreoretinal interface. The measurement scale in the instrument was calibrated for the axial length to be read directly off the photographs in mm, on the assumption of a hypothetical common speed of 1550 metres/second for ultrasound in ocular tissues. To allow for several factors which tend to give undermeasurement a correction factor of 0·25 mm was added to the axial length measurement. The figure of 3·19 mm was taken as the distance from the vertex of the cornea to the anterior vertex of the IOL, as this is an accepted figure for the style of IOL used.

Calculation was performed by a Wang 2200T computer by means of Binkhorst's formulae.[2] The first formula gave the IOL power for postoperative emmetropia:

$$D=\frac{1336\,(4r-a)}{(a-d)\,(4r-d)}.$$

D=power of IOL in aqueous (dioptres); r=corneal radius (mm); a=axial length (mm); d=postoperative anterior chamber depth plus corneal thickness.

The second formula gave a prediction of the postoperative refraction to be expected with any stated power of IOL:

$$R_S=\frac{1336\,(4r-a)-D(a-d)\,(4r-d)}{1336\,[v\,(4r-a)+0{\cdot}003ar]-D(a-d)\,[v\,(4r-d)+0{\cdot}003dr]}.$$

R_S=spectacle refraction (dioptres); v=back vertex distance (metres).

Cataract extraction was personally performed by a microsurgical technique with general anaesthesia and hyperventilation. Limbal incision was made ab externo under a limbal-based conjunctival flap. After a single peripheral iridectomy α-chymotrypsin was instilled and 8/0 virgin silk sutures (usually 5) inserted across the wound. The lens was extracted by cryoprobe and acetycholine instilled to constrict the pupil and reconstitute the anterior chamber. A Rayner-Binkhorst iris-clip lens was inserted by the closed-chamber technique, with avoidance of corneal contact. A loose 10/0 Ethilon safety-sling suture was placed through the upper anterior loop of the IOL and the margin of the peripheral iridectomy at the junction of the outer and middle thirds of the iris. The wound was closed with particular attention to suture tension to minimse induced astigmatism. The post-

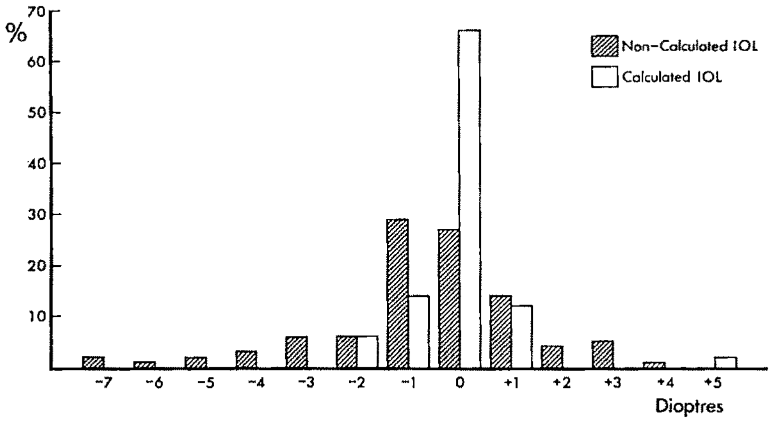

Fig. 2 *The postoperative refractions (spherical equivalent) for the control and calculated IOL groups.*

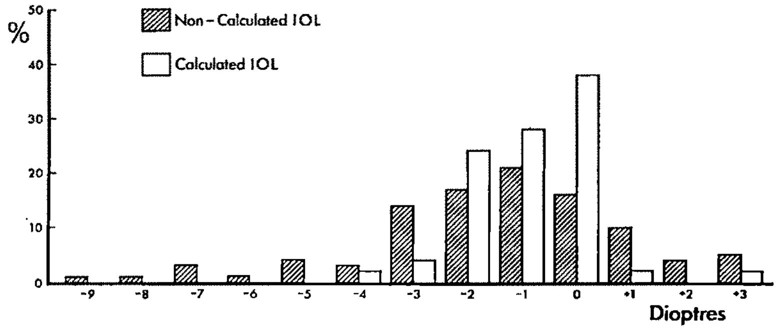

Fig. 3 *The postoperative refractions (spherical power) for the control and calculated IOL groups.*

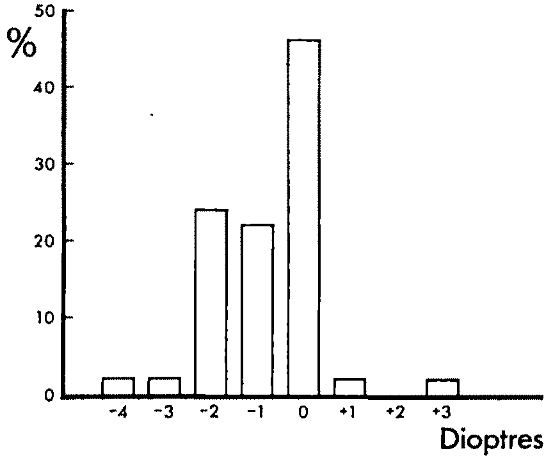

Fig. 4 *The differences in dioptres between the calculated predictions of postoperative refraction and the actual postoperative refractions (spherical power) in the calculated group.*

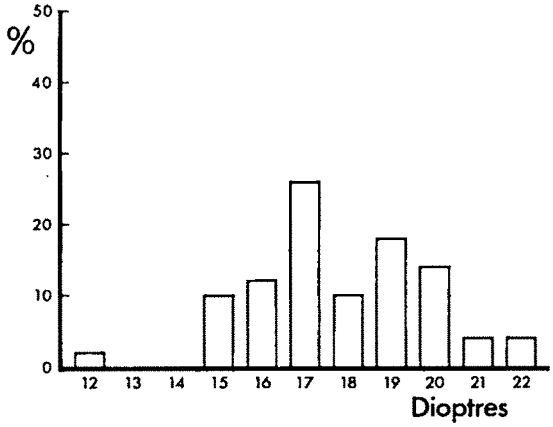

Fig. 5 *The powers of IOL (dioptres in aqueous) used in the calculated group after calculation for emmetropia.*

operative refraction was recorded when the refraction had stabilised and the first postoperative spectacles were prescribed at about the sixth postoperative week.

The postoperative refractions in terms of spherical equivalent (after conversion to plus cylinder form) and spherical power were compared for the control and calculated groups and the accuracy of prediction of postoperative refraction assessed for the calculated group.

Results

RESIDUAL REFRACTION

The postoperative refractions for the 2 groups are compared in Fig. 2 in terms of spherical equivalent. 70% of the control eyes were within the ±1 D and 80% were within the ±2 D range from emmetropia, while 92% of the calculated eyes were within the ±1 D and 98% within the ±2 D range from emmetropia. For the ±1 D range this difference is statistically significant, with $p<0{\cdot}01$ by the chi-squared test, and for the ±2 D range this difference is statistically significant with p abs $\simeq 0{\cdot}0004$ by exact probability testing. The single calculated eye with significant postoperative ametropia (+5 D) was noted preoperatively to have keratometry of doubtful accuracy because of corneal scarring.

Fig. 3 presents the postoperative refractions in terms of spherical power. 47% of the control eyes were within the ±1 D and 67% were within the ±2 D range from emmetropia, while 68% of the calculated eyes were within the ±1 D and 92% within the ±2 D range from emmetropia.

The mean astigmatism (±SD) for the calculated group was 2·0±1·4 D.

CALCULATED PREDICTION

The difference between the calculated predictions of postoperative refraction and the actual spherical power is shown in Fig. 4. 70% of the predictions were within the ±1 D range and 94% within the ±2 D range from the actual postoperative refraction.

The distribution of IOL powers used in the calculated group after calculation for emmetropia is shown in Fig. 5, and they ranged from +12 to +22 D.

Discussion

If one regards a random postoperative refractive error within the ±2 D range of spherical equivalent as acceptable, an IOL of standard +19 D power leaves 20% of eyes with ametropia greater than these limits, and some surprisingly large refractive errors are to be expected. The use of IOLs of calculated power almost eliminates significant postoperative ametropia and gives the surgeon control over the postoperative refraction.

In this study the calculated prediction tended to be biased towards hypermetropia with mean error (±SD) of 1·0±1·4 D. The 94% within the ±2 D range compare favourably with the 93% reported by Kraff *et al.*[3] and the 96% reported by Maloney *et al.*[4] within 2 D of prediction, the 97·2% reported by Johns[5] within 2·5 D, and the 97% reported by Clevenger[6] within 3 D of prediction.

There are a number of limitations to the accuracy of IOL calculation and prediction of refraction.[1] Clinical instruments for the measurement of axial length by ultrasound have an accuracy of about 0·1 mm and poor technique will reduce this accuracy. Keratometry has an accuracy of about 0·1 mm and depends on instrument calibration and fixation. The postoperative anterior chamber depth cannot be measured preoperatively and a suitable figure has to be assumed according to the style of IOL implanted. The ultimate effects of errors of these magnitudes on the postoperative refraction are shown in Table 1 and if additive will amount to a spectacle error of about 1·0 D.

The accuracy of calculation and prediction of refraction is also limited by postoperative astigmatism. Part of the astigmatism is inherent in the corneal curvatures and part is induced by surgery. The latter may be minimised but not eliminated by careful surgical technique.

Table 1 *The effects of errors in axial length, keratometry, and postoperative anterior chamber depth on the final spectacle refraction*

Axial length	0·1 mm=0·25 D
Keratometry	0·1 mm=0·50 D
Anterior chamber depth	0·1 mm=0·25 D

In view of these several limitations there is at present no justification for the use of IOLs in steps of less than 1 D (which is equivalent to about 0·75 D in the spectacle refraction) despite the misleading apparent accuracy of calculations made to several places of decimals.

Biometry and the calculation of IOL power are simple procedures requiring keratometer, ultrasound instrument, and a programmable calculator or access to a computer. The technique carries no hazard to the patient and gives better postoperative refraction results than the implantation of IOLs of standard power. The surgeon has control of the postoperative refraction and can predict and avoid unwanted ametropia.

I thank the Department of Medical Illustration at St James's University Hospital for the preparation of illustrations.

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Binocular interactions in normal and anomalous binocular vision: effects of flicker

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SUMMARY Temporal modulation thresholds were determined for monocular viewing and for binocular viewing of stimuli presented in phase or in counterphase to each eye of observers with normal binocular vision and those lacking stereopsis. The results showed that in individuals with normal binocular vision sensitivity was much greater for in-phase than for counterphase stimulation at low temporal frequencies, but that this superiority declined at higher temporal frequencies. Averaged across frequencies, binocular sensitivity for in-phase stimulation was 40–50% higher than monocular sensitivity. In contrast, in the observers lacking stereopsis the ratios of binocular in-phase/monocular sensitivity averaged 1·02, and there were no significant differences in sensitivity to in-phase and counterphase stimulation. This failure of binocular integration at threshold does not result from differences in transmission time between the 2 eyes. However, while individuals lacking stereopsis showed an absence of binocular interaction for uniform-field flicker at threshold, they showed suprathreshold dichoptic temporal frequency masking which was similar to that found in normal persons.

Sherrington's research on the integrative action of the central nervous system[1] led him to hypothesise that, if the physiological activity of each eye was combined at a neural locus common to the 2 eyes, then perception of flicker during binocular viewing of in-phase light flashes should persist well beyond the fusion of flicker with monocular viewing, while a pattern of intermittent illumination presented in counterphase (180 degrees out of phase) to the 2 eyes would reduce or eliminate the perception of flicker. To test this hypothesis he compared the frequency at which flicker disappeared (CFF) when repetitive flashes were presented simultaneously (in phase) to the 2 eyes with the CFF obtained when the flashes were presented in counterphase to the 2 eyes. Sherrington found that the CFF for simultaneous flicker was only about 3% higher than the CFF for counterphase flicker, and concluded that no physiological interaction of consequence occurred between the signals from the 2 eyes. Several subsequent experiments have also shown small but significant differences between CFF for in-phase and counterphase stimulation.[2 3]

De Lange[4] demonstrated that visual sensitivity to time-varying stimuli can be best determined by sinusoidally modulating the brightness of a stimulus about a constant average level. By determining the depth of modulation required for the perception of flicker at different temporal frequencies he determined a temporal modulation sensitivity function (or De Lange function). Recent investigations of flicker sensitivity using the approach of De Lange have shown that, in the temporal contrast domain, when the stimuli to the 2 eyes were in phase, binocular sensitivity was greater than monocular sensitivity for lower temporal frequencies, but this difference in sensitivity decreased at higher frequencies. Moreover, when the stimuli were in counterphase, binocular sensitivity was less than monocular sensitivity at low frequencies but not at high frequencies.[5–7] Thus, while Sherrington's hypothesis was correct, CFF may have been a rather insensitive measure of binocular interaction.

Persons lacking stereopsis due to early strabismus or amblyopia fail to show binocular summation on a variety of psychophysical threshold tasks.[8–10] One possible explanation for the reduced or absent binocular summation is suppression. Suppression in strabismus is most marked when the 2 eyes are presented with similar contours[11 12] and requires a short latent period in order to become manifest.[11]

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Clinically, brief exposures and/or rapid flashing of the stimuli are strategies commonly utilised to minimise or eliminate the suppression.[11] [13] Therefore it is likely that the temporal parameters of the stimuli presented to the 2 eyes might influence the degree of binocular summation found in persons with abnormal binocular vision. In the studies reported here we determined temporal modulation sensitivity functions for stimuli presented in phase and out of phase to the 2 eyes of persons with normal and abnormal binocular vision. This type of stimulus allows the determination of binocular interactions over a wide range of temporal frequencies and has the additional advantage of being less susceptible to differences in acuity or accommodation than patterned stimuli.

Materials and methods

Stimuli were generated on 2 matched cathode ray tube displays (Tektronix 5103 N) which were viewed in a mirror stereoscope. The screens were masked to form a 6° by 6° square. A small square served as a fixation point in the centre of each screen, and horizontal and vertical nonius lines on the 2 screens were used to ensure that the stimuli were presented to corresponding points in the 2 eyes and that fusion was maintained throughout the experiments. Cover testing in the apparatus was used to further ensure appropriate binocular alignment.

The Z axis of each oscilloscope could be modulated in luminance sinusoidally about a mean luminance of 10 cd/m^2, which remained constant throughout the experiments.

EXPERIMENTS

Three separate experiments were conducted.

Experiment 1. Temporal modulation sensitivity: In phase versus counterphase.

In the first experiment temporal modulation sensitivity functions were measured for temporal frequencies from 1 Hz to 40 Hz. At each temporal frequency the temporal contrast of the modulation was adjusted via a logarithmic attenuator. Thresholds were determined by an ascending method of limits, and for each contrast threshold the series of 5 measurements yielded a standard error of less than 5%. Thresholds were determined for binocular stimulation in phase and 180° out of phase (counterphase), and also monocularly, with the untested eye viewing a homogeneous field of the same mean luminance. The order of temporal frequencies and conditions was randomised. Trials in which one of the nonius lines was not seen, owing to suppression, were excluded from data analysis.

Experiment 2. The effect of small interocular delays.

Binocular temporal modulation sensitivity was determined for 1 Hz and 10 Hz flicker presented in phase to the 2 eyes, and with interocular phase lags of 15° to 180° in 15° increments. The order of presentation of the stimuli was randomised, and monocular thresholds were also obtained for each eye during the same experimental session.

Experiment 3. Suprathreshold temporal frequency masking.

Temporal modulation sensitivity functions were determined monocularly by an ascending method of limits. At each temporal frequency the test stimulus was presented for 4 seconds. The observer was instructed to make a Yes/No response. Modulation was increased in 0·05 log unit steps from below threshold until 2 consecutive positive responses were obtained. Threshold was taken as the first of 2 consecutive positive responses. Blank trials were included as a control for response bias. Five monocular thresholds were obtained at each temporal frequency under each of 2 conditions (1) while the untested eye viewed a blank field of the same average brightness, and (2) while the untested eye viewed a suprathreshold uniform field flicker 'mask' at 5, 10, or 20 Hz, modulated about 1 log unit above threshold.

SUBJECTS

Six observers between 20 and 30 years of age were tested. Two of the authors, each with normal binocular vision and stereopsis, served as normal participants. The other 4 observers all showed an absence of stereopsis (determined via the random dot E test, the Wirt stereotest, and the American Optical nearpoint vectograph). Two of the observers were classified as monofixators, and 2 had a small angle alternating esotropia. All had at least 20/30 or better acuity in the nondominant eye. All observers had clear media and normal fundi and were appropriately corrected for refractive error during the experiments.

Results

EXPERIMENT 1

Modulation sensitivity determined with in-phase (open circles) and counterphase (filled circles) flicker are shown for a normal observer in Fig. 1A. The ratio of in-phase to counterphase sensitivity at each frequency is shown by the circles below. At low frequencies (<5 Hz) this observer is considerably more sensitive to in-phase than to counterphase flicker, with the ratios decreasing monotonically at higher frequencies. The triangles in the same figure show the ratio of binocular sensitivity for in-phase flicker to the mean monocular sensitivity. For this normal observer binocular in-phase/monocular ratios averaged across frequencies was 1·51. This is similar to the $\sqrt{2}$ improvement for binocular viewing found

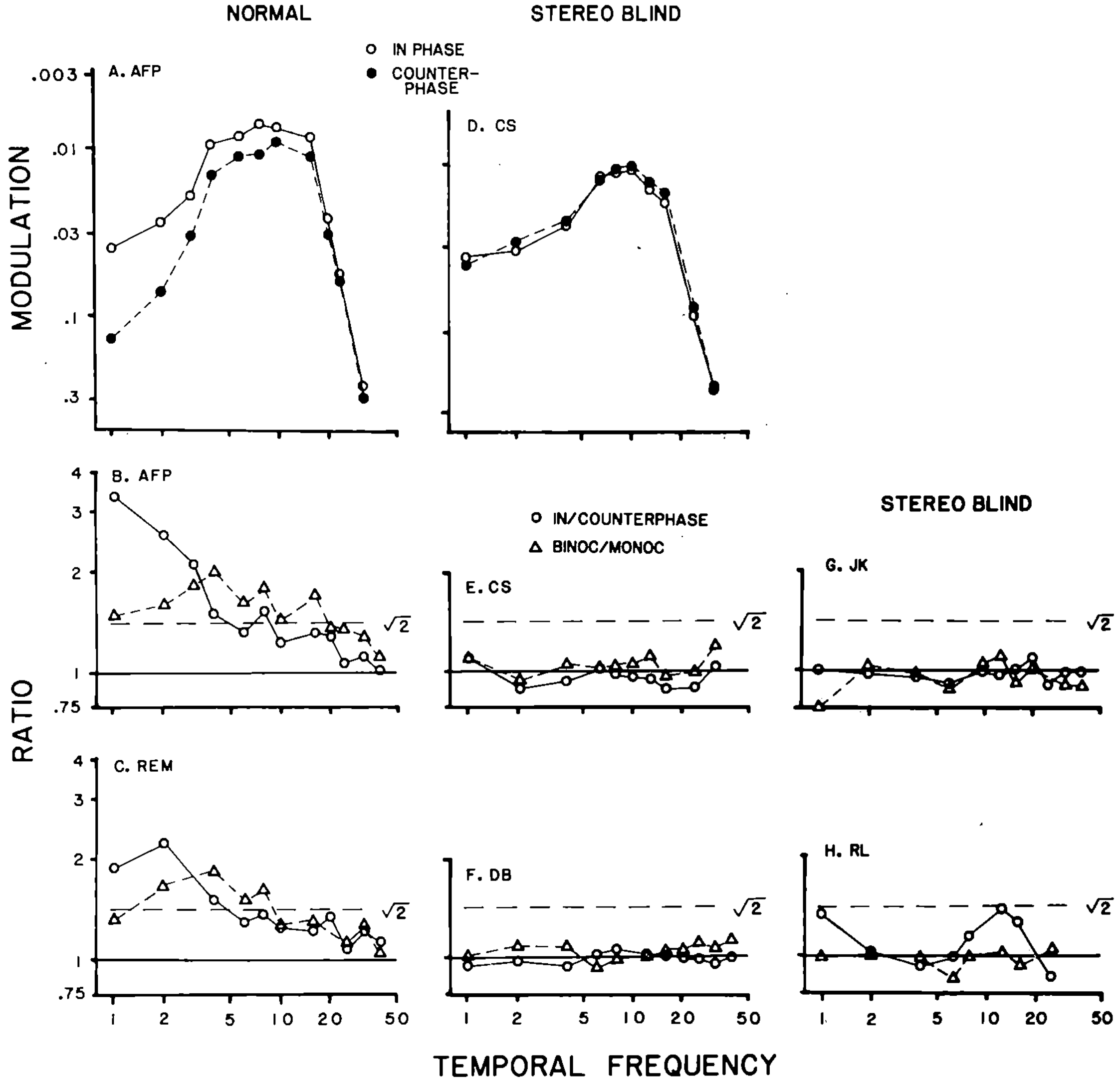

Fig. 1 *Modulation thresholds for binocular in-phase (open circles) and counterphase (solid circles) uniform field flicker for normal observer AFP* (A) *and for observer CS with anomalous binocular vision* (D). *The ratio plots below show the ratio of in-phase/counterphase sensitivity (circles) and the ratio of in-phase binocular/monocular sensitivity (triangles). The ratio plots on the left* (B *and* C) *are for the normal observers; those on the right* (E-H) *are for the anomalous observers.*

for spatial stimuli by Campbell and Green,[14] a value which is predicted by assuming that the signals from the 2 eyes are summed and that the signals contain noise that is uncorrelated between the 2 eyes. This value is shown by the dashed line. It should be noted that the binocular in-phase/monocular ratio is also strongly dependent upon temporal frequency; thus the approximation to $\sqrt{2}$ may be somewhat misleading. Nevertheless the strong binocular summation, particularly at low temporal frequencies, is greater than would be predicted on the basis of probability and therefore must reflect neural summation.[14] Similar results are shown for the other normal observer as a ratio plot in Fig. 1C.

The data reported thus far also suggest that in normal observers binocular interactions show strong temporal specificity. There is little difference between binocular in-phase sensitivity and either monocular or binocular counterphase sensitivity at high frequencies. However, at low frequencies there is considerable interaction between the 2 eyes, with binocular in-phase sensitivity enhanced, and counterphase sensitivity reduced as compared with monocular sensitivity. These results are in agreement with previous studies of normal binocular interactions.[5–7]

Data for an observer with anomalous binocular vision (CS) are shown in Fig. 1D. The sensitivity of this observer to both in-phase and counterphase flicker was quite similar, and did not differ significantly from the monocular sensitivity, as can be seen in the ratio plot below (Fig. 1E). Since the monocular thresholds for each eye of all of the observers were essentially equal, we have averaged the monocular thresholds for the 2 eyes. Essentially the same results were obtained by comparing the binocular thresholds with those of either the dominant or the nondominant eye. Similar results were obtained for the other observers with anomalous binocular vision, and their ratio plots are shown in Figs. 1F, G, and H. For the observers lacking stereopsis the binocular/monocular ratio averaged 1·02, and the binocular in-phase/counterphase ratios averaged across frequencies averaged 1·01. For only 1 anomalous observer (RL, Fig. 1H) did the ratios of in-phase/counterphase stimulation exceed 1·1. This occurred at 2 distinct temporal frequencies, 1 Hz and 12·5 Hz. Interestingly, at these 2 frequencies the monocular and binocular in-phase sensitivities were essentially equal. Thus these results may reflect inhibitory interactions at these 2 frequencies in the counterphase condition. However none of the observers with anomalous binocular vision showed significant binocular summation at any temporal frequency.

EXPERIMENT 2

One possible mechanism for the failure of observers without stereopsis to show binocular summation could be a difference in transmission time between the 2 eyes, so that the in-phase signals to the 2 eyes do not reach the brain simultaneously. Since no binocular summation was evident in the 180° out-of-phase condition, we performed a second experiment in order to test more carefully the possibility that small interocular delays may preclude binocular summation. Thresholds were determined for 1 Hz and 10 Hz stimuli with different phase lags. This procedure allowed us to investigate the effects of delays as brief as 4 ms. Fig. 2A shows the binocular/monocular ratio for normal observer AFP for the 1 Hz (open symbols) and 10 Hz (filled symbols) stimuli. The abcissa shows the phase lag of the stimulus presented to the left eye with respect to that presented to the right eye. The lower 2 abcissas show the relative delay in milliseconds for the 10 Hz and 1 Hz stimuli. For this observer, when the stimuli were in phase, there was substantial binocular summation, which

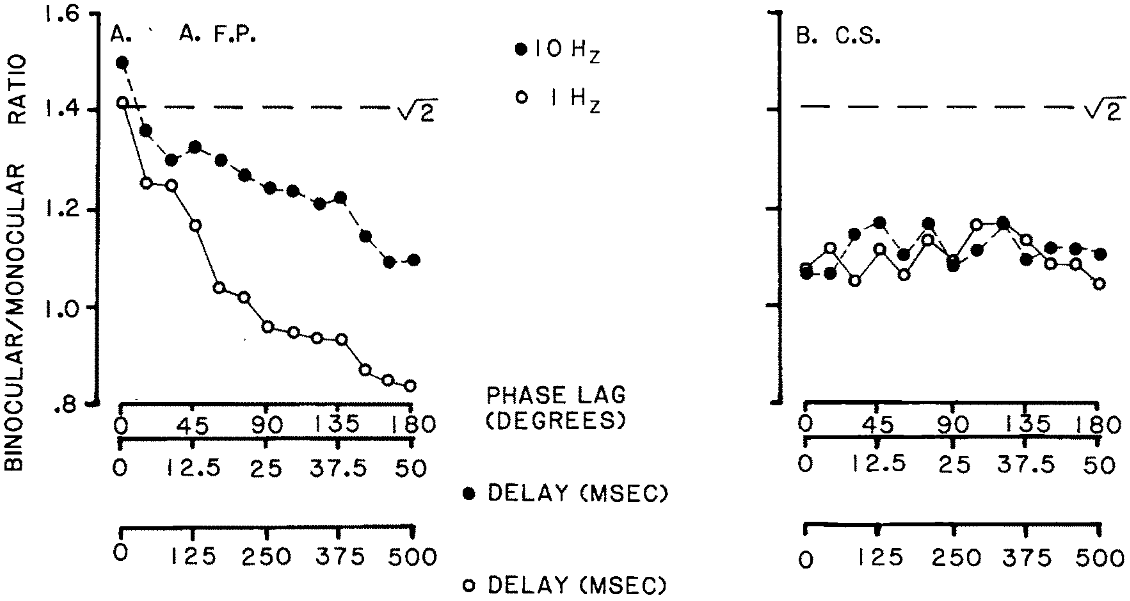

Fig. 2 *The binocular/monocular sensitivity ratio as a function of phase for 1 Hz (open circles) and 10 Hz (solid circles) modulation for normal observer AFP* (A) *and anomalous observer CS* (B). *The abscissa shows the phase lag of the stimulus to the left eye with respect to that of the right eye. The lower 2 abscissas show the relative delay (in milliseconds) for the 10 Hz and 1 Hz stimuli.*

decreased as the phase lag between the 2 eyes increased. This decrease in binocular summation as a function of phase lag was more rapid at 1 Hz than at 10 Hz, since the delay is 10 times greater at 1 Hz than at 10 Hz for a given phase lag. At 10 Hz the data fell to a binocular/monocular ratio of 1·1 with a 180° phase lag. This 10% improvement of binocular performance might be predicted on the basis of probability summation.[10] Interestingly, the 1 Hz data fall below 1·0 when the signals to the 2 eyes are more than 90° out of phase, showing significant cancellation of the signals.

Data for an anomalous observer (CS) are shown in Fig. 2B. At both frequencies the binocular/monocular ratio hovered between 1·05 and 1·17 with an average of about 1·1. There was no delay which produced any significant binocular interaction, excitatory or inhibitory. Similar results were obtained by advancing the phase of the left eye signal with respect to the right eye. We should point out that while this observer showed a binocular/monocular summation ratio which was consistent with probability summation both at 1 Hz and 10 Hz, this was not true for all temporal frequencies either for this observer or across observers as illustrated in the ratio plots of Fig. 1D-H. Most of the anomalous observers showed binocular/monocular ratios which were closer to 1·0 over the range of frequencies tested. The data presented here are in agreement with studies of spatial contrast sensitivity in observers with abnormal binocular vision in showing an absence of binocular summation.[8 9] The present results extend this absence of binocular summation into the temporal frequency domain, and further suggest that the absence of summation does not result from different transmission times between the 2 eyes.

EXPERIMENT 3

The results of experiments 1 and 2 indicate that anomalous observers lack excitatory binocular interactions at threshold. However, it has recently been reported that observers with abnormal binocular vision do show binocular interactions in suprathreshold dichoptic masking tasks.[9] In these experiments a suprathreshold masking grating presented to one eye raised the contrast thresholds for gratings presented to the fellow eye within a narrow range of spatial frequencies and orientations centred about the spatial frequency and orientation of the mask. The results of the present experiment show that analogous binocular interactions occur in the temporal domain.

These results are shown for a normal observer (filled circles) and for a stereoblind observer (open circles) in Fig. 3. The results for each of the 3 masking frequencies are shown separately. In order to show the masking effect clearly the data are plotted as the ratio of unmasked to masked modulation sensitivity (i.e., the ratio of sensitivity when the untested eye viewed a blank field to that obtained when the untested eye viewed a suprathreshold uniform field flicker mask). The error bars on the right of the graphs show 2 standard deviations. For each masking frequency the flicker mask presented to the untested eye produced substantial elevation of the flicker thresholds of the tested eye. While the peak threshold elevation in each case coincided with the masking frequency, the masking is considerably broader than occurs in the spatial domain. Thus the 5 Hz mask has a width at half strength of more than 4 octaves. The 10 and 20 Hz masks appear to produce somewhat more peaked threshold elevation functions. What is of greater interest, however, is the similarity of these dichoptic temporal masking functions for the normal and stereoblind observers, in both magnitude and extent. Similar results were obtained regardless of which eye viewed the test and masking stimuli, and the data in Fig. 3 are representative of the functions obtained for the other normal observer and each of the observers with anomalous binocular vision.

Discussion

The results of these experiments suggest that persons with normal binocular vision show strong integration of the signals from the 2 eyes and that the nature of binocular interactions is highly dependent upon temporal frequency. These results are in agreement with several recent studies of binocular interactions for time-varying stimuli in normal persons.[5–7] However, individuals lacking stereopsis fail to show significant binocular interactions at threshold for uniform field flicker at any frequency, even though these stimuli were equally detectable by each eye individually. This failure of binocular integration at threshold does not appear to result from differences in transmission time between the 2 eyes.

The present results are in agreement with previous reports suggesting that persons lacking stereopsis fail to show binocular summation at threshold.[8–10] The presence of suprathreshold dichoptic masking in the temporal domain, as well as in the spatial domain,[9] suggests that these anomalous observers do retain binocular interactions which are similar to those found in normal persons. The broadly tuned dichoptic flicker masking found in these experiments may be analogous to the finding that adaptation to sinusoidal flicker produces a temporary elevation in the temporal contrast threshold. This adaptation effect is much less specific than that occurring for spatial stimuli,[15 16] though the effects of successive adaptation reportedly did not transfer interocularly.[15]

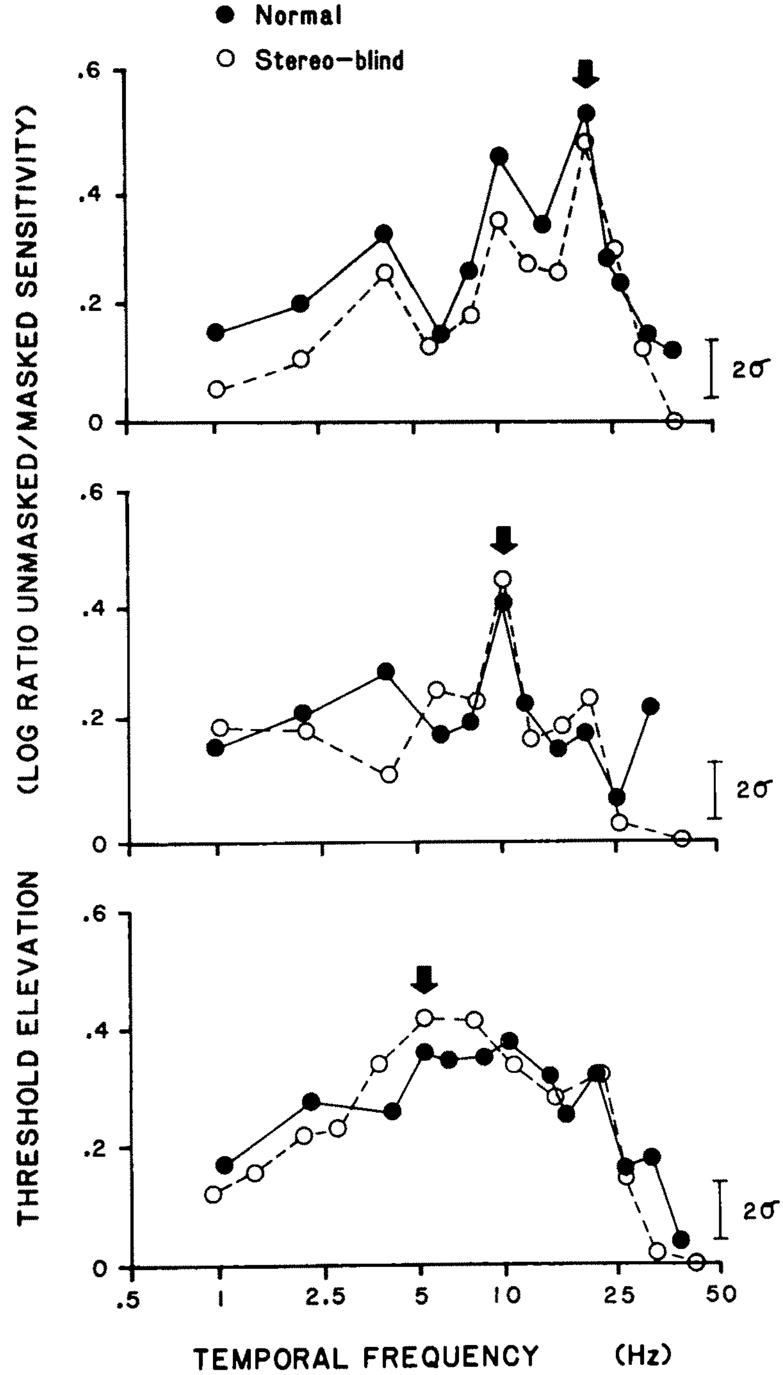

Fig. 3 *Threshold elevation produced by the 20 Hz (top), 10 Hz (middle), and 5 Hz (bottom) temporal masks (i.e., ratio of log modulation sensitivity with a homogeneous background to that with the uniform field flicker background about 1 log unit above threshold) for normal observer REM (filled circles) and stereoblind observer CS (open circles). The error bar shows 2 standard deviations.*

Conclusions

The present results, in conjunction with the recent reports that some stereoblind observers do show interocular transfer of the threshold elevation aftereffect[17 18] and may show binocular interactions in the steady state visual evoked potential elicited by high-contrast gratings,[19] suggest that some binocular neurons survive the disruptive effects of early abnormal binocular visual experience. It appears that the processes involved in these interactions are not as susceptible to the effects of early visual experience as the processes involved in binocular summation or stereopsis.

We thank Dr Ronald Harwerth for his valuable discussions and advice.

This work was supported by research grant RO1 EY 01728 from the National Eye Institute, Bethesda, Maryland, USA.

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The sensitive period: transfer of fixation after occlusion for strabismic amblyopia

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SUMMARY Of 2649 patients with strabismic amblyopia who attended clinics between 1941 and 1978, 1904 patients were reviewed. Of these, 115 patients had transfer of fixation after occlusion. These were analysed according to the type of transfer of fixation and relation to occlusion and age. The period of maximum sensitivity to short periods of occlusion extended to 18 months, declining to about 30 months of age. Sensitivity to occlusion reaches low levels about the age of 5 to 5½ years, though it is still present to some degree, especially in patients with relatively good visual acuity of 6/36 or better. The upper limit of the sensitive period was found to be about the end of the seventh year of age.

There is a clearly defined period during early postnatal life of experimental animals during which the visual system is particularly susceptible to alterations in the visual experience. A few days of visual deprivation during the early life of kittens[1 2] and monkeys[3–8] resulted in amblyopia and histological changes in the lateral geniculate body and the visual cortex.

In man the situation is less clear. Clinical experience indicates that stimulus deprivation amblyopia in children can result from opacities in the media or other forms of visual deprivation.

Congenital cataracts are known to be associated with poor vision.[9–11] Children with bilateral congenital cataracts, if treated and corrected early, have better visual results.[12] In unilateral cases it is generally agreed that early correction does not seem to have an effect on the visual outcome, but some authors have reported better visual results with early treatment and correction.[13 14] If deprivation in patients with unilateral cataract occurs between 6 and 30 months of age, counting fingers is the best visual acuity achieved. If deprivation starts between 3 and 10 years of age, visual acuity decreases at a slower rate and is more likely to respond to total full-time occlusion.[14] Occlusion in these patients is most effective before the age of 4 years.

Von Noorden and Maumenee[15] observed that amblyopia is more likely in patients who develop cataracts before the age of 6 years, with reversible amblyopia up to the age of 4 to 6 years. Von Noorden stated that the upper limit of the sensitive period is 51 months[16] and that amblyopia is reversible up to the age of 5 years.[5] A more recent view is that the age of sensitivity may extend from birth to approximately 7 years of age and is greatest in the first 2 years of life.[17] Von Noorden and Crawford[18] suggest that the plastic age may extend from birth to the end of the fifth year of life and amblyopia rarely occurs after traumatic cataract in children as old as 7 years. It has been found that corneal opacities after 7 years of age have no significant influence in the development of amblyopia and fixation patterns after keratoplasty.[19]

Awaya *et al.*[20] reviewed 19 cases of amblyopia with a history of unilateral occlusion of the eye (mostly for about one week following lid surgery). Sixteen cases were within 13 months of age. The remaining 3 were within 36 months of age. In another article Awaya *et al.*[21] reviewed a total of 100 cases of occlusion amblyopia after correction of entropion or other minor lid surgery, after unilateral congenital or traumatic cataract, or after small punctate posterior polar cataract or linear scar of the corneal endothelium and found no irreversible decrease in visual acuity in patients who had short-term lid closure after 18 months of age, with a peak effect between 6 and 9 months. For longer periods of occlusion the critical period may extend to 24 months of age. When occlusion of the sound eye was started before the ninth year of age, visual recovery was poor in approximately 50% of cases, and all the patients who started occlusion of the sound eye after 9 years of age had showed a poor recovery of their visual acuity.

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Visual evoked responses (VER) have been used as a reliable estimate for measuring visual acuity in infants.[22 23] They can also give valuable information on the development of vision in man.[24 25] From the visual evoked response it is generally agreed that the visual system in man undergoes rapid maturation in the first year of life, and the visual acuity approximates adult level by 24 months of age. In the same way the amplitude and wave form of VER change to that of adult configuration by 24 months of age.[26] However, Sokol and Jones[25] reported that minor changes in VER wave form continue until the age of 5 to 6 years and there is little change after 7 years. Arden and Barnard[26] using VER found that the plasticity of the visual system is retained till the age of 5–11 years.

Interocular transfer (IOT) of the tilt after-effect was used to assess binocularity. It is highly correlated with stereopsis, which is a common clinical index of binocular function. By relating the degree of IOT of the tilt after-effect to the date at which strabismus was first seen and corrected the strabismus was found to have maximum effect on this measurement between 1 and 3 years of age, and continues with exponentially decreasing strength until the age of 8 years.[27] These authors suggested that immediate corrective surgery is not necessary to maintain cortical binocularity when the esotropia is of late onset, of 4 years and over. Also, by measuring IOT in children whose squint developed at different ages but was corrected by surgery, the end of the critical period for the development of the binocular vision in man was found to be about 2–2·6 years.[28]

RESPONSE TO OCCLUSION

Occlusion has long been used in the treatment of strabismic amblyopia and other forms of amblyopia in children. It has also been known that response to occlusion was dependent on age.[9 29 30] Occlusion amblyopia and transfer of fixation sometimes occurs during occlusion therapy for strabismus; this has been recognised since 1948.[9] Hardesty[31] states that over 6 years of age there was probably no danger of producing occlusion amblyopia of a marked degree with patching for several months. Other various authors reported or reviewed similar cases after occlusion, though in general not great in numbers. Goodier[32] reviewed 21 patients over 3 years old; none were older than 5 years.

The fact that a switch of fixation occurs at all, especially if it either requires occlusion for its reversal (temporary) or is not affected by such occlusion (permanent switch), implies that the neurological mechanisms of fixation must be of sufficient plasticity in those patients to permit considerable realignment. The evidence suggests, as expected, that this plasticity is greater in young children, who require less occlusion, than in older children to produce a switch of fixation, but can nevertheless be present sufficiently in some children up to a certain age.

This article is a report on 115 patients who had transfer of fixation, with or without amblyopia, who were studied in an attempt to define the sensitive period in man. The type of transfer of fixation, whether transient, temporary, or permanent, may be an important indicator of susceptibility to occlusion. Other factors related to the transfer of fixation, such as visual acuity, binocular single vision before and after occlusion, refractive errors, etc., will be dealt with in a subsequent publication.

Materials and methods

All the patients recorded under the heading of strabismic amblyopia in the Orthoptic Department of the Sheffield Area Health Authority (Teaching) were reviewed. Patients were selected on the following criteria:

(1) Before occlusion a measurable strabismus had been present, without alternation of fixation.

(2) Occlusion had been either: (*a*) total continuous occlusion of light and form as a patch; (*b*) intermittent or partial physical occlusion, sometimes with periods of total continuous occlusion.

Patients who had other than physical occlusion at any stage were not included in the analysis, but in view of the particular interest of those in whom the transfer of fixation was not reversible, one such patient who had had atropine occlusion during part of his occlusion period is included in the analysis; another patient in whom the type of occlusion was unknown was included in the *b* category.

(3) After occlusion there was transfer of fixation, without alternation, to the nonoccluded eye for either a limited period or until the patient was discharged.

The selected patients were analysed according to whether the transfer of fixation was (*a*) transient, that is, reversed to the original fixation or alternated without further occlusion, in subsequent visit or visits; (*b*) temporary, that is, reverted to the original fixation or alternates after various forms of occlusion of the newly fixing eye; (*c*) permanent, that is, reversed squint permanently to the originally fixing eye.

A total of 2649 patients were listed under the heading of strabismic amblyopia, but only 1904 notes were found. These patients attended during the period 1941–78, when the study was initiated. Though some were still attending at the time of review, the final outcome of occlusion could be determined.

Results

One hundred and fifteen patients fitted the criteria for transfer of fixation, 25 had transient switch of fixation,

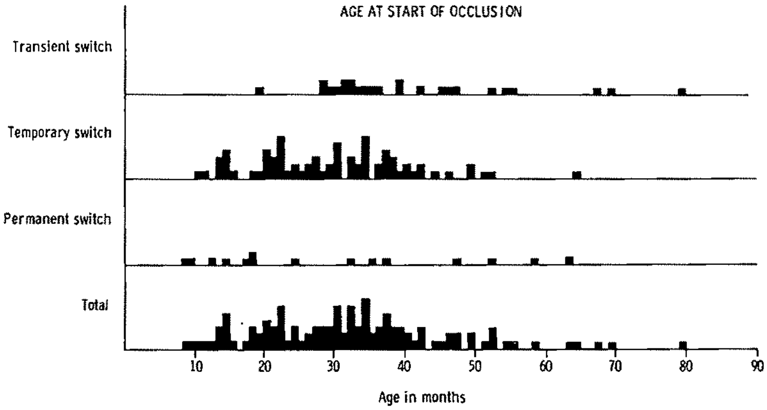

Fig. 1 *Age at the start of occlusion for patients with transfer of fixation according to the type of switch. Most were under 5½ years of age, and older patients tended to have transient switch. The number of the patients at the younger end of this figure is probably determined by the number of patients occluded at such an early age rather than by sensitivity to occlusion.*

75 had temporary switch, and 15 had permanent switch.

In 48 of the 75 patients with temporary switch further occlusion was delayed until further visit or visits which confirmed the transfer of fixation, but 27 patients were treated by immediate occlusion of the fixing eye. Some of these might, if left without occlusion, have shown only transient switch of fixation, so the distinction between transient and temporary switch is somewhat blurred.

Of the 15 patients with permanent switch only 5 never switched back or alternated with further occlusion. The remainder switched back at some time to the originally squinting eye, but, after further different types and methods of occlusion, switched back to have strabismus in the originally good eye for a few years before discharge.

TYPE OF OCCLUSION

Transfer of fixation may follow either total continuous occlusion or various combinations of partial or intermittent occlusion. The majority of the latter had a period of initial total continuous occlusion, then had a break in occlusion or changed to milder forms. There is an apparent tendency for patients with permanent transfer to follow partial and/or intermittent occlusion (Table 1).

In 2 patients in the temporary group and two in the permanent group transfer of fixation followed surgery on the originally fixing eye, the squint having become alternating. There were no surgical complications, and presumably the change in fixation was due to lid swelling, photophobia, or lid closure acting as a temporary form of occlusion.

Table 1 *Type of occlusion and the type of switch*

Type of occlusion	*Pattern of switch of fixation*		*Total*
	Transient or temporary	*Permanent*	
Total continuous occlusion	59	4	63
Partial and/or intermittent occlusion	41	11	52
Total	100	15	115

AGE OF BEGINNING OCCLUSION

The age of occlusion of 115 patients ranged from 9 months to 6 years and 8 months (Fig. 1), with a mean of 33 months. Abot 88% of the patients were aged 4 years or less. A total of 14 patients switched fixation at an age of occlusion of over 4 years. All except 4 had a relatively good visual acuity of 6/36 or better in the amblyopic eye at the start of occlusion. One of those 4 was aged 5 years and 4 months and had a permanent switch of fixation after 7 successive months of mostly total continuous occlusion.

The age of occlusion for the patients with permanent switch of fixation ranged from 9 months to 5 years and 4 months, with a mean of 25 months. Those with temporary switch had a mean of 31 months. Patients with transient switch had a mean of 37 months. The last group were on average older than the other 2.

AGE OF TRANSFER OF FIXATION

The age of transfer of fixation was taken as the age at the midpoint of the period of occlusion during which the transfer occurred. This ranges from 9 months to 6 years and 10 months (Fig. 2). The graph for the age of switch of fixation (Fig. 3) shows that the peak of the permanent switch cases was in the second year of life, the temporary switch cases at the third year, and those of the transient switch at the fourth year of life. Fig. 2 shows only that one patient had transient switch of fixation below the age of 30 months, and this patient, at the age of 20 months, had only one week of total continuous occlusion. So younger patients tended, if they transferred fixation at all, to have at

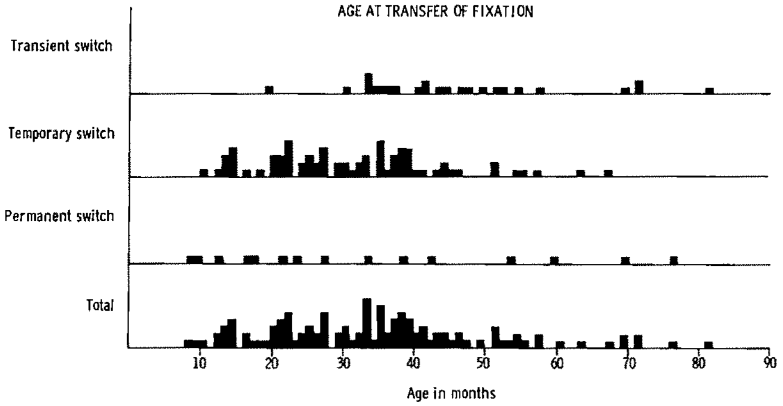

Fig. 2 *Age at transfer of fixation taken as the age at the middle of the last period of occlusion immediately before the visit during which switch of fixation was demonstrated. Most patients were under 6 years of age.*

least a temporary, if not a permanent, transfer. All the 3 groups showed a decrease in the number of patients at the end of the fifth year of life.

DURATION OF OCCLUSION

The relationship between the duration of occlusion and the age of occlusion cannot be usefully assessed in those patients who had various forms of intermittent and/or partial occlusion. The relationship in those who had continuous total occlusion is shown in Fig. 4. The continuous line shows the period of occlusion during which the change of fixation occurred, its upper end giving the total period of occlusion: switch of fixation could have occurred at any time during this visit. This figure shows a wide range of scatter, but this could be explained by variations in the state of visual acuity and fixation before occlusion, binocular single vision, refractive state, duration of squint, and the type of switch produced, in addition to how strictly the patient carried out the instructions for total continuous occlusion.

Nevertheless, there is an obvious relationship between the age of occlusion and the duration of occlusion, the reversal of fixation occurring quicker in the younger age group. The youngest patient to switch after total continuous occlusion was 10 months and the oldest was 4 years and 7 months at the start of occlusion. Most of the patients below 2 years of age switched fixation after one visit of total continuous occlusion and mostly within 2 weeks of occlusion. There is a noticeable increase in resistance to occlusion after this period, and resistance to occlusion reaches high levels after the age of 4 years.

Children with permanent switch of fixation are in many ways the most interesting, since it implies that permanent damage could be produced to fixation and visual acuity. All these patients had energetic occlusion in an attempt to reverse the transfer of fixation. The age of occlusion at which switch occurred in this group extended to 64 months of age (Fig. 5), and the age of transfer extended to 77 months of age. Patients under the age of 18 months needed a relatively short time of occlusion to transfer fixation. Four patients with permanent transfer switched after total continuous occlusion only; all were below the age of 18 months.

Five of these patients never switched back or

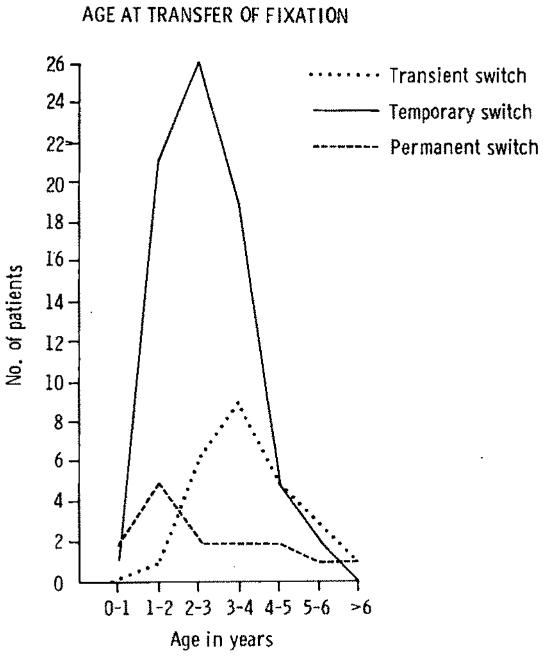

Fig. 3 *Graph of the age at transfer of fixation according to type of switch. Notice patients with permanent switch of fixation had a peak age between 1–2 years. Temporary switch patients between 2–3 years and those with transient switch between 3–4 years of age.*

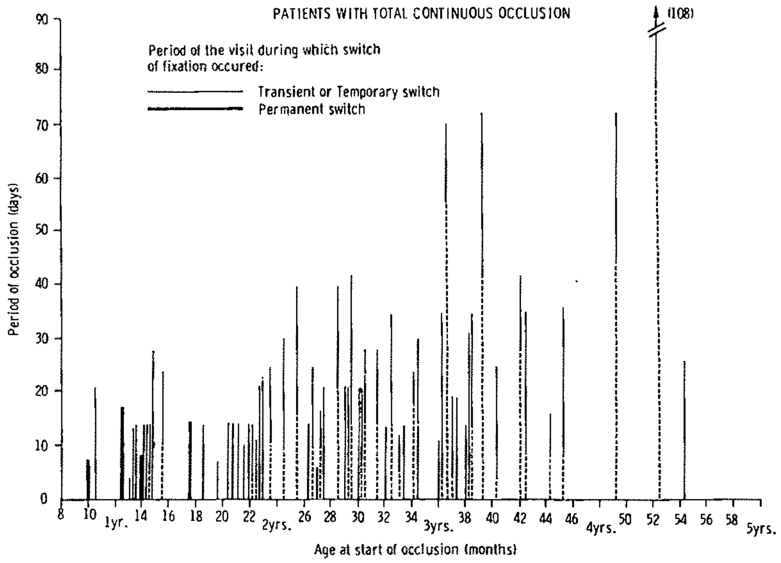

Fig. 4 *Patients who switched fixation after total continuous occlusion only. Four patients under the age of 18 months had permanent switch, all other patients had either temporary or transient switch. The duration of occlusion increases with age, with variations which could be explained in most cases by the refractive state, visual acuity, and fixation prior to occlusion and the type of switch produced. None of the patients were older than 4½ years.*

alternated after the initial transfer of fixation, in spite of reversal of occlusion, indicating a considerable damage to the fixation mechanisms. Three of these patients were below 14 months of age and 2 had obvious prolonged periods of occlusion (Fig. 5).

Discussion

It must be remembered that this is a retrospective study and therefore subject to the limitations of any such study. Moreover, the exact type and duration of occlusion was determined by the individual orthoptist concerned, subject to the general policy of the department, and may therefore have varied considerably between orthoptists and at different times. The intervals between visits during occlusion was sometimes quite long, sometimes doubtless due to the failure of the patient to attend, so that the exact duration before switch of fixation occurred is sometimes rather uncertain.

Development of fixation mechanisms on the other hand is a separate process from development of many other visual functions, and its process of maturation may or may not reflect the general maturation of the visual system. Nevertheless some conclusions can be tentatively drawn.

The period of susceptibility to switch of fixation after occlusion was found to be between 9 months and 6 years and 10 months of age. The lower limit is probably determined in this study by the number of patients occluded at such an early age rather than by the sensitivity to occlusion during this period, which can be outlined as follows:

The most sensitive part (critical period) was up to 18 months of age, with patients under 14 months being the more so. Considerable sensitivity extends to 24 or 30 months of age. This is supported by:

(*a*) The 3 patients under 14 months of age in the permanent switch group, switched fixation after short period of occlusion and never switched back or alternated. (*b*) Four patients who had permanent switch of fixation after total continuous occlusion were under 18 months of age. (*c*) Those patients below 18 months of age in the permanent switch group needed relatively shorter periods of occlusion to switch. (*d*) Most of the patients under 2 years old in the total continuous occlusion patients switched fixation within one visit and mostly within 2 weeks of occlusion. (*e*) The peak of permanent switch group was in the second year of life. (*f*) Transfer of fixation below 30 months of age was permanent or temporary rather than transient.

These findings fit those in previous reports.[14 17 20 21 26 28] This is also supported by the findings that most of the human visual system appears to be anatomically adult by the age of two years.[33]

The sensitivity reaches low levels at about the age of 5 to 5½ years (after the fourth year) of life, though still present to some degree, especially in patients with relatively good visual acuity of 6/36 or better. This is supported by:

(*a*) Few patients switched fixation beyond 5–5½ years of age. (*b*) Few patients switched fixation with total continuous occlusion after 4 years of age. (*c*) All patients with permanent switch of fixation had their age of start of occlusion below 5½ years. (*d*) Older

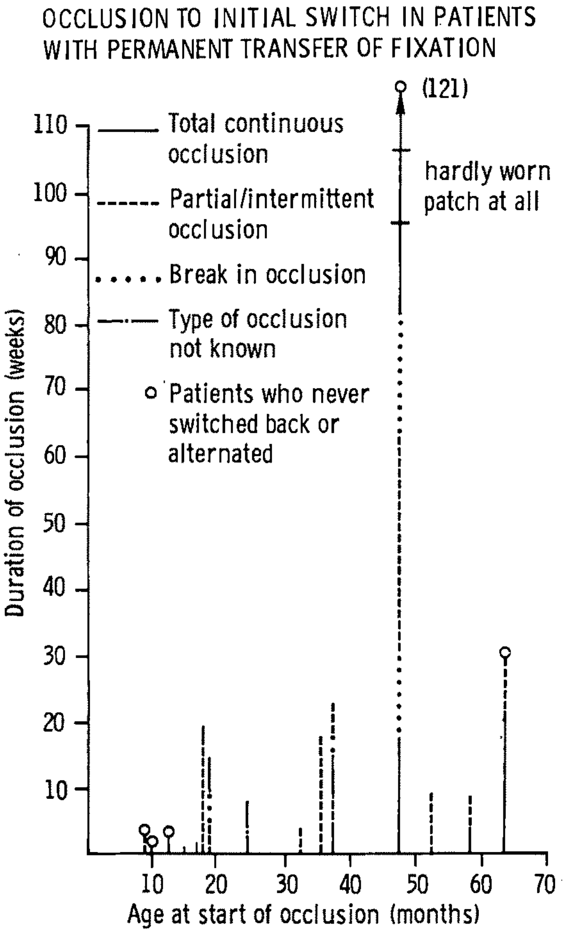

Fig. 5 *Period of occlusion in patients with permanent switch of fixation. Patients under 18 months of age had relatively shorter periods of occlusion. Five patients never switched back or alternated, 3 were under 13 months of age, and 2 had prolonged initial total continuous occlusion. None of the patients were older than 5½ years of age at the start of occlusion.*

patients, over 4 years of age, tended to have transient switch and have good visual acuity of 6/36 or better before occlusion.

These findings fit those recorded in previous reports.[5, 14–16, 18, 25, 27, 31] It might be of interest to mention that the normal human newborn child has a typical brain mass of 350 g and at 1 year old of about 500 g, and that the brain, particularly the cerebral cortex, continues to grow rapidly in the first 3 years of life—the period of most rapid learning. By the age of 6 years the mass of the brain is 90% of its adult value of 1375 g.[34] This, though, indicates that the general development of the brain may have a relation to the development of the visual system.

The upper limit of the sensitive period is about the end of the seventh year of age. This fits previously reported findings.[17–19, 25, 27]

I am indebted to Mr Alan Stanworth for his encouragement and valuable contributions and comments all through this article. My thanks also to Mr A. J. Dark, Mr I. M. Strachan and other consultant staff at the Royal Hallamshire Hospital for encouragement and for allowing me to include their patients, to Mr R. Mapstone for his encouragement and to Orthoptic Department staff for their co-operation.

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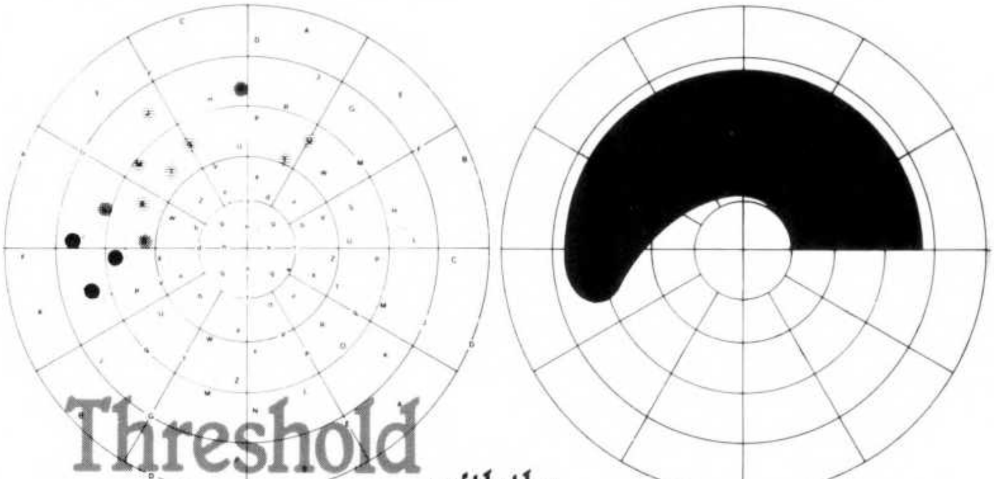

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Lacrimal canalicular obstruction following chickenpox

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SUMMARY Three cases of unilateral epiphora following an attack of chickenpox were studied. Each patient was a child who was in good health prior to the onset of the attack. During the illness each had ocular symptoms suggesting local infection from the virus. A dacryocystogram revealed obstruction of the common canaliculus in each case caused by a fibrotic scar. All cases responded to appropriate surgical management.

Lacrimal canaliculus obstruction is a known complication of virus infection.[1] Although several different viral diseases have been implicated in this way, chickenpox has been mentioned only sparingly in the medical literature as having such a complication. Three cases were recently observed and provided the opportunity to examine this more closely. The results are reported here.

Materials and methods

During the past year 3 cases of common canaliculus obstruction following an attack of chickenpox presented at the Lacrimal Clinic of Moorfields Eye Hospital, City Road, London. All were children who were in good health and asymptomatic before the onset of the illness.

In addition to the general ocular examination a dacryocystogram (DCG) was performed on each patient to identify and localise the obstruction. All patients have undergone surgery. Either a dacryocystorhinostomy (DCR)[2] with resection of the obstruction from within the sac or a Barrie Jones type of canaliculodacryocystorhinostomy (CDCR)[3] was performed. In all patients the system was left intubated with polyethylene tubing (no. 10 Portex) for 3 months. A tissue specimen from one of the cases was sectioned for histological study and examined for evidence of the virus.

CASE REPORTS

Patient 1. A 10-year-old boy presented with a 14-month history of epiphora in his right eye following immediately after an attack of chickenpox. During the illness vesicles were present on the eyelids, and the eyes were 'red and irritable' with crusting on the lashes and considerable tearing. The general ocular examination was normal, but an obstruction was

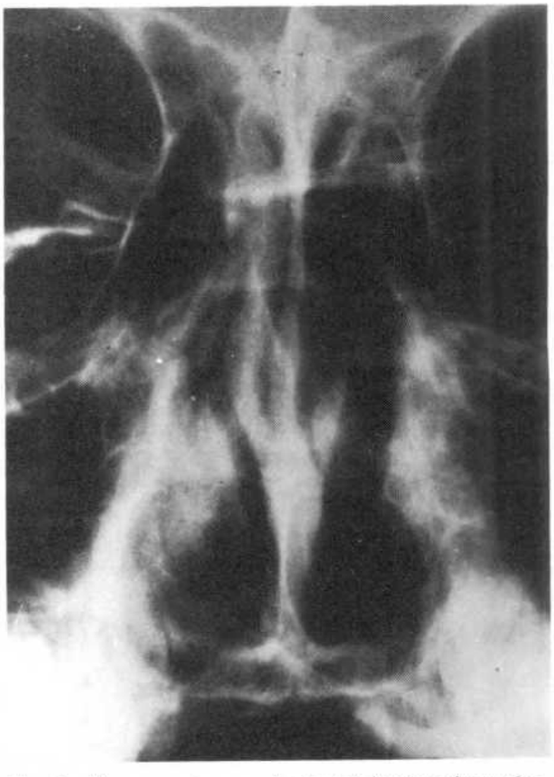

Fig. 1 *Dacryocystogram of patient 1 showing obstruction at the medial end of the right common canaliculus.*

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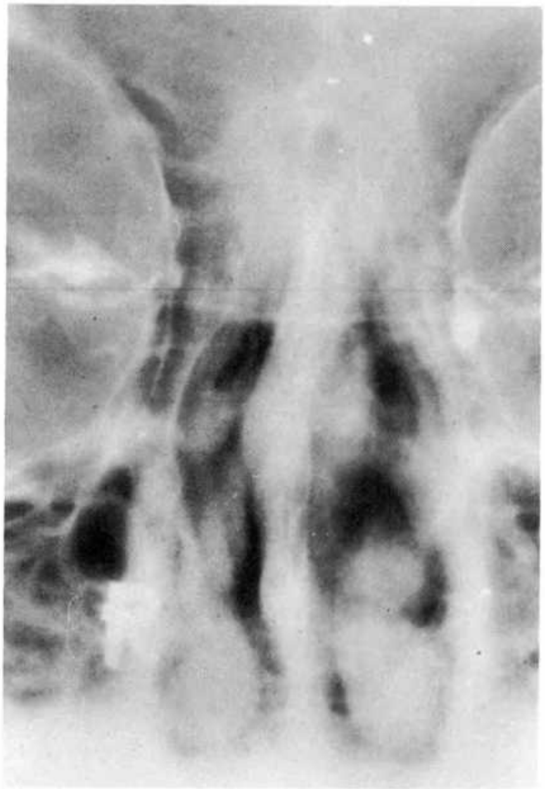

Fig. 2 *Dacryocystogram of patient 2 showing partial obstruction of the common canaliculus at its medial end in the right eye.*

found at the medial end of the right common canaliculus on the DCG (Fig. 1). At surgical operation a plaque of fibrous tissue was found to be occluding the internal opening of the common canaliculus, and this was excised from within the sac. After a conventional DCR had been completed the canaliculi were left temporarily intubated with soft polyethylene tubing for 3 months. After removal of the tubes the patient has remained symptom free.

Patient 2. A 10-year-old boy presented with an 18-month history of epiphora of the right eye that was first noted immediately following an attack of chickenpox. The eyes were 'red and irritable' during the illness, but no vesicles were noted near them. The ocular examination was unremarkable except for partial obstruction at the medial end of the right common canaliculus seen on the DCG (Fig. 2). At surgery the internal canalicular opening was found to be stenosed by a fibrous scar which was excised from within the sac. A DCR was completed and the canaliculi temporarily intubated with the polyethylene tubing for 3 months. The symptoms disappeared afterwards. There were no complications.

Patient 3. An 11-year-old girl presented with a 2-year history of epiphora of her right eye that began immediately after an attack of chickenpox. The eyes were described as being 'red and irritable' during the

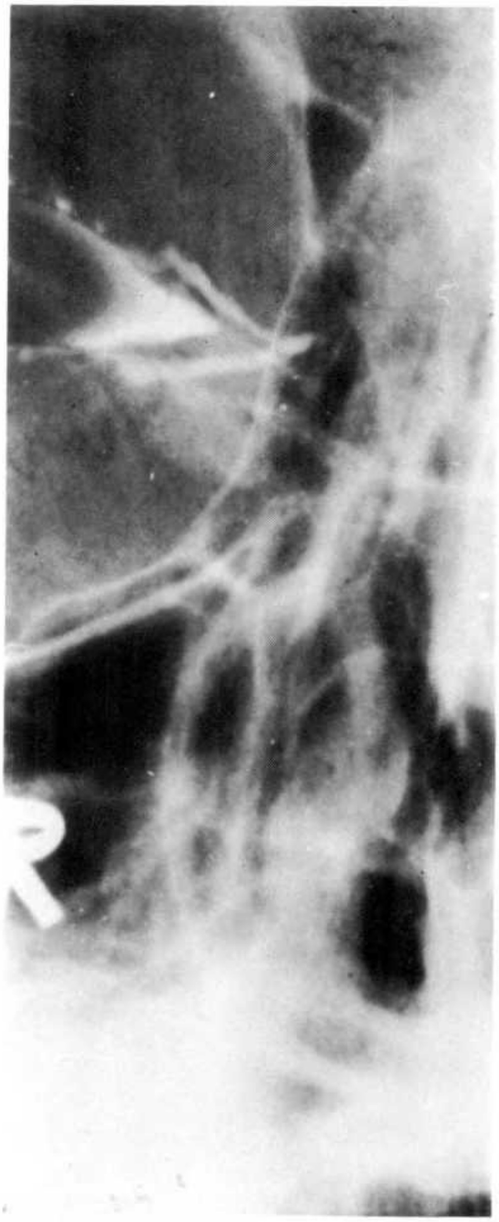

Fig. 3 *Dacryocystogram of patient 3 showing obstruction of the right common canaliculus at its medial end.*

illness, with vesicles on the eyelids and on the bulbar conjunctiva. The general eye examination was normal, but an obstruction of the medial end of the common canaliculus was seen on the DCG (Fig. 3). Because of the experience in the previous 2 cases the common canaliculus was dissected and exposed prior to opening the tear sac. A fibrotic scar, which was found again to involve the internal opening of the common canaliculus, was resected. A CDCR was then completed by anastomosing the divided common canaliculus to the nasal mucosa, the lacrimal sac being used as a bridge. The system was left intubated with the soft polyethylene tubing for 3 months. There were no complications.

The excised tissue from patient 3 was sent for histology and virus identification studies. It was found to be composed of fibrous scar tissue but was otherwise unremarkable. No giant cells or intracellular inclusion bodies were found. Indirect immunofluorescent staining tests with human antisera were negative for virus, including the varicella-zoster (V-Z) virus. Antibodies in the patient's blood for V-Z virus indicated past infection.

Results

There were no unusual systemic symptoms during the chickenpox attack in any of these patients. The eyes in all 3 cases, however, were 'red and irritable,' and in 2 of the 3 cases the parents recalled that vesicles were present on the eyelids or on the conjunctiva. Apart from the epiphora beginning immediately after the attack there were no other complications. The health of each of the patients has returned to normal.

The features common to these 3 patients were: an ocular inflammation complicating an attack of chickenpox, unilateral epiphora, and an obstruction of the lacrimal drainage apparatus which was located at the level of the common canaliculus. Although the *x*-ray appearances suggested a mucosal type of obstruction, which is usually a characteristic of chronic sac disease, surgical exploration showed this not to be present; a localised, dense fibrous scar involving the common canalicular opening was found in all cases.[4]

Discussion

The circumstances in these 3 cases enable us to conclude that the common canaliculus obstruction was the result of the chickenpox attack. That other viruses are known to act in a similar way supports this.

In its systemic manifestations chickenpox may involve almost any organ of the body,[5] though ocular involvement is rare. Griffin and Searle reported only a 4% incidence of lesions in the eye.[6] These were limited to isolated vesicular eruptions of the eyelid margin and to the conjunctiva and corneoscleral limbus. A report by Edwards[7] separated ocular involvement into 4 categories: the eyelids, the cornea and conjunctiva, intraocular complications, and neurological complications. However, there was no mention of any effects on the lacrimal system. Werb commented in passing on 'secondary infections' involving the punctum and canaliculus from chickenpox but gave no further information about them.[8]

Attempts to identify the presence of V-Z virus in the fibrous scar excised from patient 3 gave negative results, but this does not exclude a cause-effect relationship. McSorley *et al.*[9] examined new lesions during the active, infectious phase of chickenpox but found only a few which reacted 'weakly positive' to immunofluorescent testing, while the majority gave a negative reaction as had occurred in our case.

There is no doubt that identification of virus provides strong evidence of the connection between the infection and scar formation. Bouzas has shown that this relationship can still be deduced from the particular circumstances of the case.[10] It was seen in the present cases that:

(1) there was no epiphora prior to the onset of the infection with its ocular involvement;

(2) the tearing was noted immediately after the illness had resolved;

(3) formation of fibrous scar tissue is a characteristic result of inflammation in mucous membranes caused by viruses.

This result has been previously recognised, and a review of cases from the Lacrimal Clinic at Moorfields Eye Hospital showed that virus diseases were the most common cause of lacrimal canaliculus obstruction.[11]

The ocular symptoms indicate that during the active phase of the illness the infection also involves the eyes themselves. The causative agent for chickenpox, the varicella-zoster (V-Z) virus, is an encapsulated DNA virus.[12] It acts on host tissue by entering the nucleus of the cell and after replicating causes the cell to rupture and release the newly created particles. These new virus particles can then infect other cells, perpetuating the cycle.[13]

This virus is very susceptible to DNA inhibitors such as the ophthalmic antiviral agents idoxuridine, cytosine arabinoside, and adenine arabinoside.[12] In the event of ocular involvement during an attack of chickenpox, local treatment with these antivirals may prevent lacrimal complications and their associated morbidity.

We thank Professor S. Darougar and Dr P. Walpita of the Virus Laboratory, Institute of Ophthalmology, London, for their help with the virus identification studies, and Miss Catherine Elliot for her assistance in preparing the manuscript.

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Book reviews

Quantitative Layer-By-Layer Perimetry: An Extended Analysis. By JAY M. ENOCH, C. R. FITZGERALD, E. C. CAMPOS. Pp. 232. $29·50. Grune and Stratton: New York. 1981.

The introduction over the past 25 years of new anatomical, physiological, and biochemical techniques has added enormously to our knowledge of the complexity of the visual pathway, while the clinical localisation of pathological processes in the retina has been enhanced by fluorescein angiography and electrodiagnostic procedures. Much of the work of Professor Enoch and his group has been concerned with the development of noninvasive psychophysical tests of visual function, which not only provide information to be correlated with the more recent anatomical and physiological studies of the normal visual processes, but also have a bearing on clinical ophthalmological practice and research. This book gives an account of this work together with an assessment of its present stage of development and the advances which may be expected from its impact on future research.

The subject matter lies in an area of specialised interest shared by visual scientists and clinicians and deals mainly with 3 procedures—a test of 'sustained-like' function, a test of 'transient-like' function, and the flashing repeat static test (FRST). The first 2 functions are described with appropriate references to the previous work of Westheimer, who studied the correlation of this type of psychophysical test of vision with the underlying physiology.

The initial step in testing is the determination of the threshold of a small test target, presented as a flashing point of light. The luminance of this target is then raised by a constant factor. In order to test the sustained-like function a surrounding background field is introduced, the luminance and area of which can be varied; measurement is made of the effect of these variations on the perception of the test-target. The level of adaptation at which the test is done is set by a large illuminated field which surrounds the background field. In order to test the transient-like function the flashing test target is surrounded by a background field bearing a windmill-shaped pattern, and measurements are made with the windmill stationary and rotating. The flashing repeat static test is concerned with the alteration in retinal sensitivity over a relatively short period of time. The apparatus needed for these tests and the methodology are described. In reading the descriptions of these tests, the clinical ophthalmologist will appreciate that they are designed to assess relatively unfamiliar factors, such as integrative activity within the retina, temporal variations, and the effect of on-off signals, rather than the more familiar ones associated with the testing of acuity and visual fields during routine clinical practice.

Of particular interest to the clinical ophthalmologist are the extensive presentations of the results obtained on various groups of patients with pathological changes in different layers of the retina and with glaucoma, the clinical details often being supplemented by illustrations of fluorescein angiography and visual fields. It is clear that the work is still in its relatively early stages, but the evidence accumulated so far may be summarised as follows. Outer retinal diseases, involving the choroid, pigment epithelium, and retinal receptors, appear not to alter the results of any of the 3 main tests. Diseases of the inner retina, that is, from the outer plexiform layer to the nerve fibre layer, cause alterations in the sustained-like or transient-like functions or in both, but the FRST is not affected. By contrast, diseases of the optic nerve beyond the nerve head, such as retrobulbar neuritis, alter the FRST but not the other functions. In open-angle glaucoma it is of interest that changes are found in the sustained-like and transient-like functions but not in the FRST.

This book is of interest mainly to 2 groups of readers, referred to, rather negatively, as the 'nonclinician' (p.19) and the 'nonpsychophysicist' (p.18). It is inevitable therefore that some material will probably appear elementary to one group and advanced to the other, but on the whole a satisfactory balance has been achieved. The general impression which the clinician may gain from the book is that, although the psychophysical tests described may be time-consuming and demand much from the patient, there is reason to suppose that their future application will be of practical clinical value in helping to demonstrate exactly where visual function is disturbed by a pathological process. Some of the basic science will be unfamiliar to the 'nonpsychophysicist' but the general presentation is interesting and stimulating. JOHN GLOSTER

Cataract Surgery and its Complications. 3rd edn. By NORMAN S. JAFFE. Pp. 611. £55·00. YB Medical Publishers: London. 1981.

This is the third edition of Dr Norman Jaffe's book, which has now become a classic. Like its predecessor it is divided into 2 main parts. The first part deals mainly with the principles of cataract surgery and the second with complications.

The first of the 10 chapters making up part 1 deals with the decision to operate. This should be read by all ophthalmologists, as it contains many useful tips on how to handle patients about to have cataract surgery and advice on postoperative management. There is also a detailed description of the evaluation of eyes with mature cataracts. The section on intraocular lenses is also outstanding, as might be expected from Dr Jaffe's great interest and experience in this field. The chapter on surgical techniques discusses in depth the older methods of extraction, such as the use of the Graefe knife and of the erisiphake, and compares the technique of sliding with tumbling. The paragraph on congenital cataract surgery is somewhat disappointing and contains vague statements such as 'the exact age at which surgery must be performed to avoid amblyopia is not known. This is probably sometime during the first year'. None of the references quoted on congenital cataracts are less than 11 years old. The chapter on the management of subluxated lenses is similarly out of date. Although it describes in detail the older methods, no mention is made of closed intraocular surgical techniques which have revolutionised the management of this very difficult problem. It is surprising that, although a whole chapter is devoted to phacoemulsification (written by Dr Charles Kelman) there is no mention of lensectomy techniques for the management of soft and complicated cataracts. The chapter on wound healing is detailed and excellent, as is the chapter on keratomileusis and keratophakia by Dr Jose Barraquer. The section dealing with postoperative corneal astigmatism is, however, of little interest to the general ophthalmologist, with its many complicated geometrical analyses.

The second part of the book, dealing with postoperative complications, consists of 21 chapters. All of the complications are discussed in detail, from common complications such as shallowing of the anterior chamber to rare ones such as epithelial invasion. The descriptions are uniformly excellent. J. J. KANSKI

Illustrated Handbook of Ophthalmology. By RUDOLF SACHSENWEGER. Pp. 164. £7·50. John Wright: Bristol. 1981.

This book, which has been translated from the original German edition, is aimed at medical and ophthalmic optic undergraduates. It will have an immediate appeal for students seeking a text to supplement their clinical teaching, for it is an attractive volume, profusely illustrated by monochrome and colour photographs and excellent diagrams.

A considerable amount of information is contained within its 150 pages, but the format is somewhat old fashioned and the overall approach too systematic. A greater emphasis on presenting symptoms and differential diagnosis would have increased the book's value to the student. The text, however, is clear, and an appropriate emphasis has been placed on medical ophthalmology with only brief accounts of surgical procedures. The translation from the original is excellent, and the book has been well edited to bring it into line with United Kingdom practice.

ROGER COAKES

Ptosis: 3rd edn. By CROWELL BEARD. Pp. 276. £35·75. C. V. Mosby: London. 1981.

This book remains the classical monograph on ptosis surgery. The format has not been altered in this new edition and the basic text is the same. The main changes are in the chapter on newer operations for ptosis. It has been updated to include many of the most recent concepts. The other chapters have also been brought up to date with the addition of several new and relevant references. The size of the book has not increased significantly, since the author has omitted some of the material that he previously published in order to make room for the new additions.

Crowell Beard has more experience in ptosis surgery than anybody else in the world and yet has the ability to present each chapter in such a clear and logical way that it is readily intelligible to anyone wishing to learn about the subject. The basic anatomy, physiology, and pathology are clearly described, and all the operations are well illustrated with excellent diagrams. There are a profusion of clinical photographs which demonstrate what may and may not be achieved with the different procedures. He has not altered his personal anecdotal style of writing, which makes the book eminently readable as a whole, while at the same time it is so well indexed that it can be used as a reference book for an opinion on any problem likely to be encountered in ptosis surgery.

This book should be read by everyone with any interest in ptosis, and those who practise ptosis surgery are strongly recommended to buy it both as a practical guide and as an up-to-date reference book. J. R. O. COLLIN

An Atlas of Ophthalmic Surgery. 3rd edn. By J. H. KING AND J. A. C. WADSWORTH. Pp. 654. £49·00. Harper and Row: London. 1981.

The coverage of the field of ophthalmic surgery in this book (its third edition) is good but at times too limited. The monochromatic illustrations are excellent and numerous, being accompanied by brief explanatory texts covering many aspects of the surgical manoeuvres involved in these operations. These texts probably fail in that they are too brief and for the student leave some questions unanswered, while the operations covered in the book are only the ones preferred by the authors; thus alternative measures are not described. The illustrations are beautiful and demonstrate the chosen steps in the operations with a rare clarity. New sections in this edition include recent advances in eye surgery. IAN DUGUID

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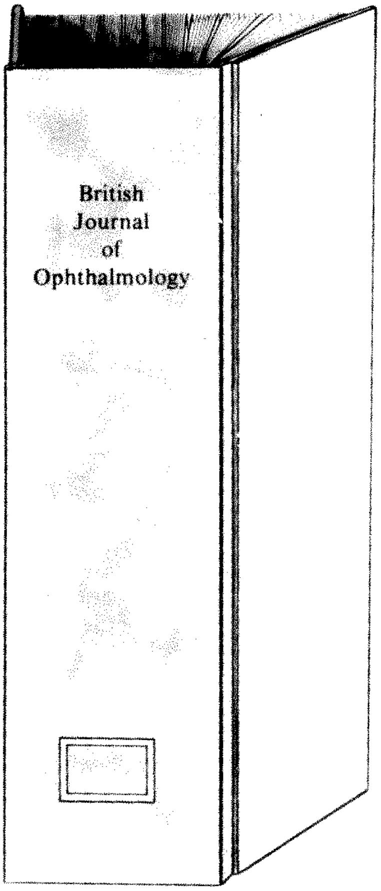

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ASTM CODEN BJOPAL 66 (1) 1-76 (1982) ISSN 0007-1161

British Medical Association Tavistock Square London WC1H 9JR

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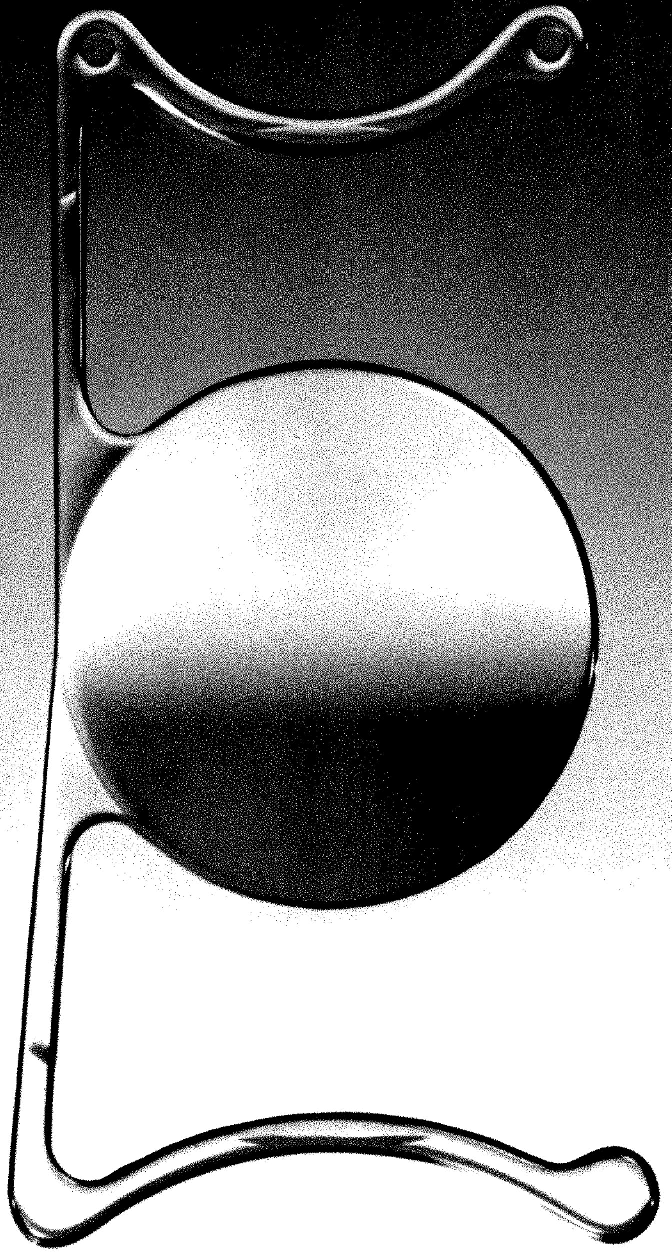

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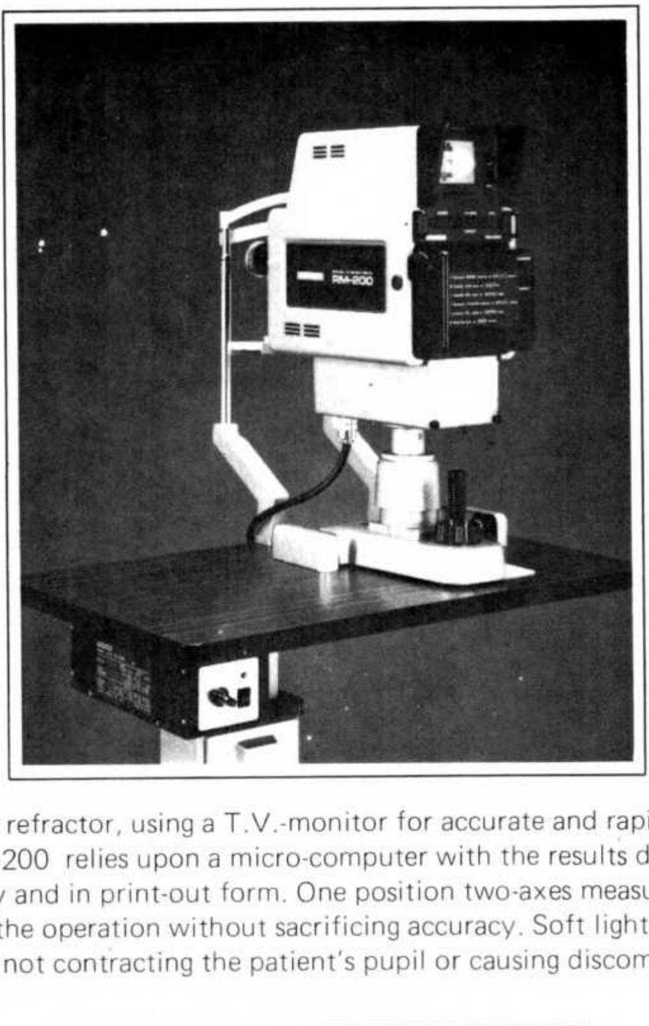

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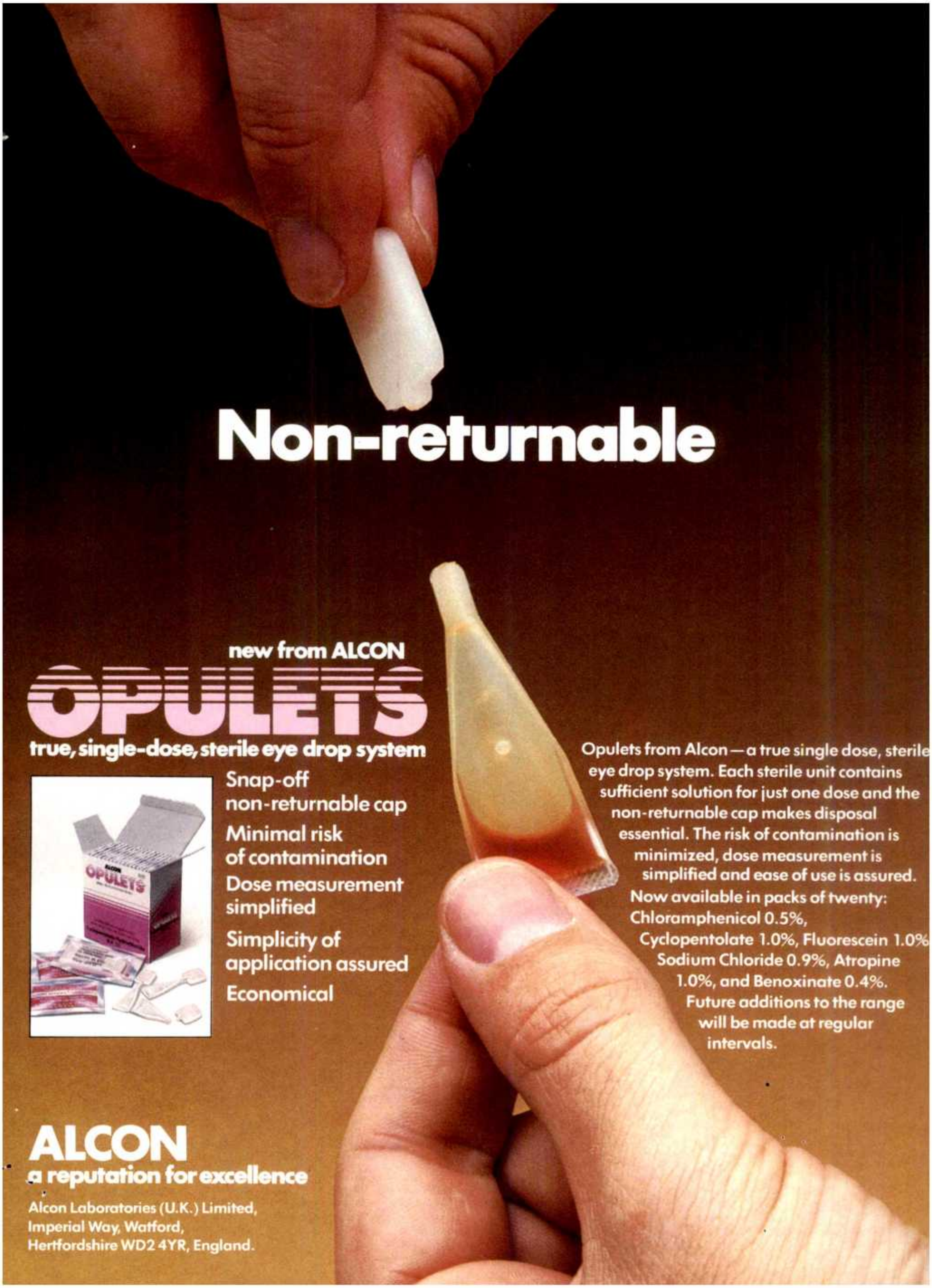

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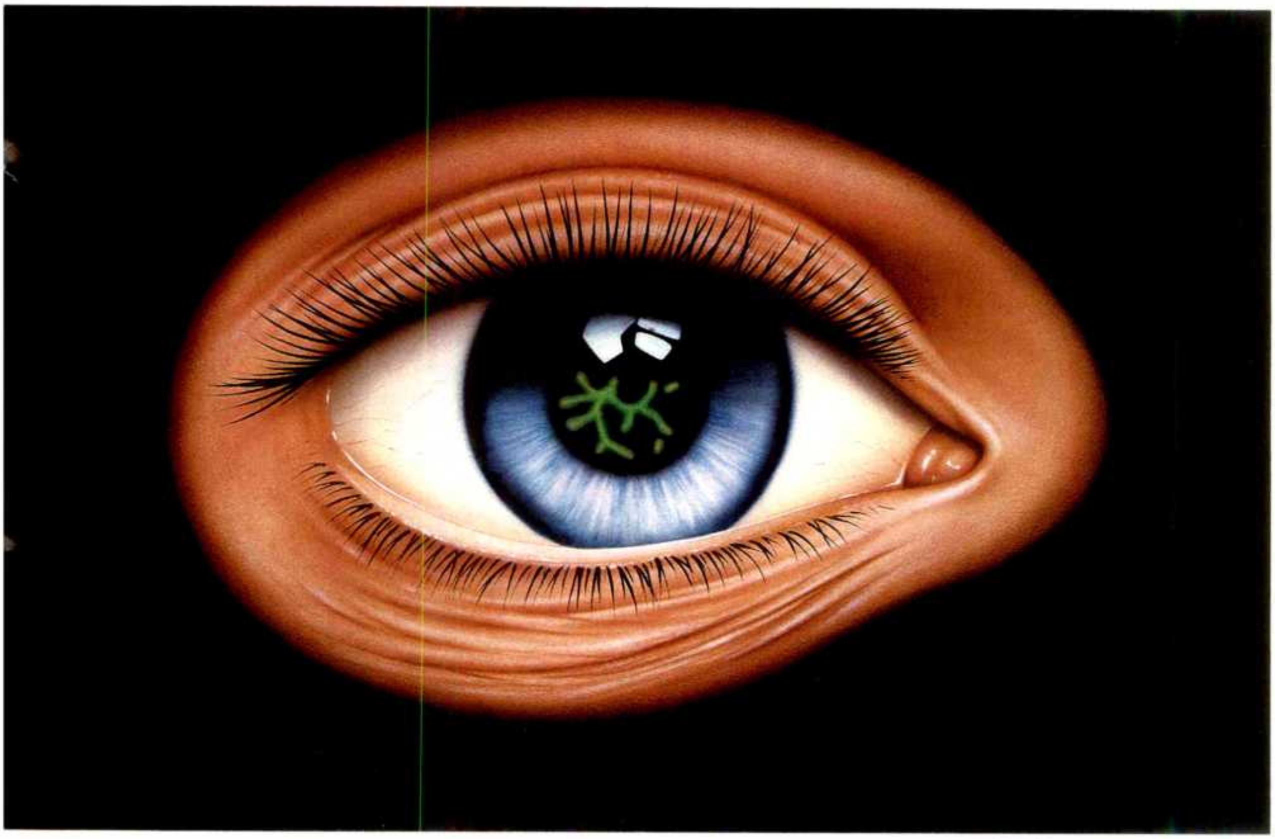

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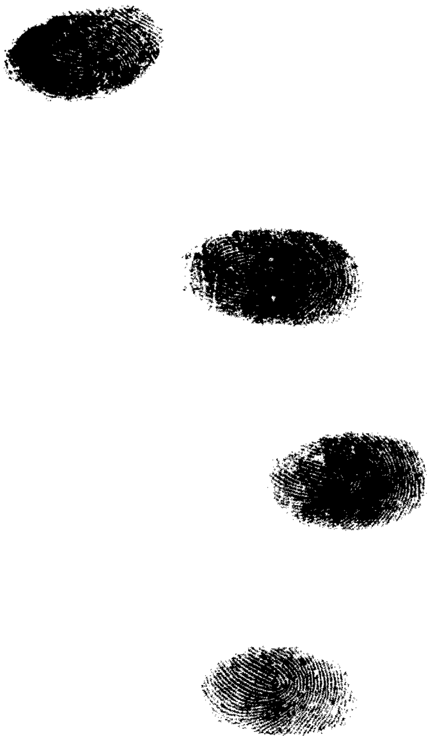

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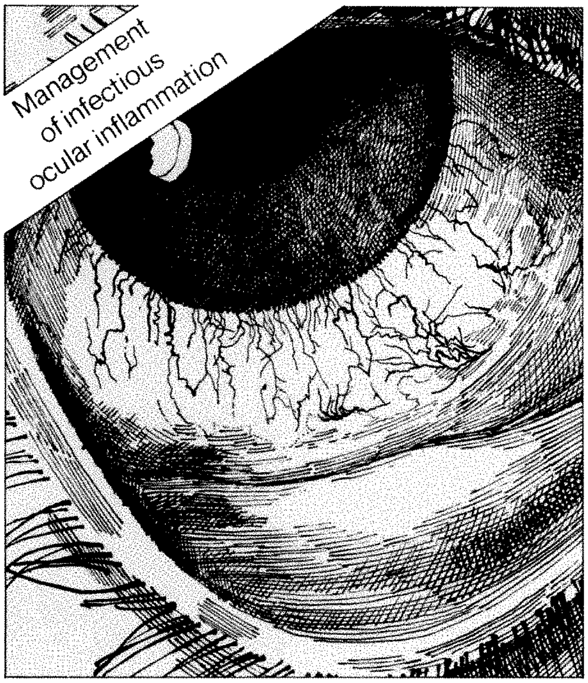

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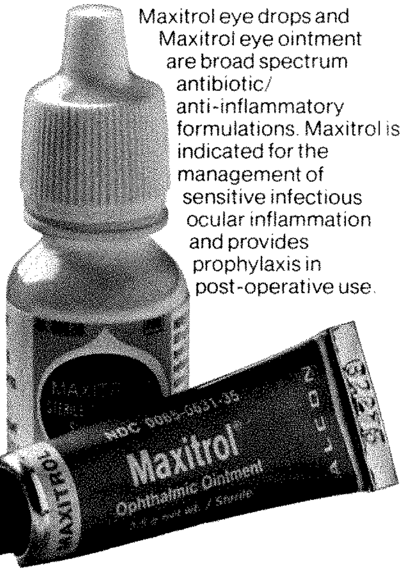

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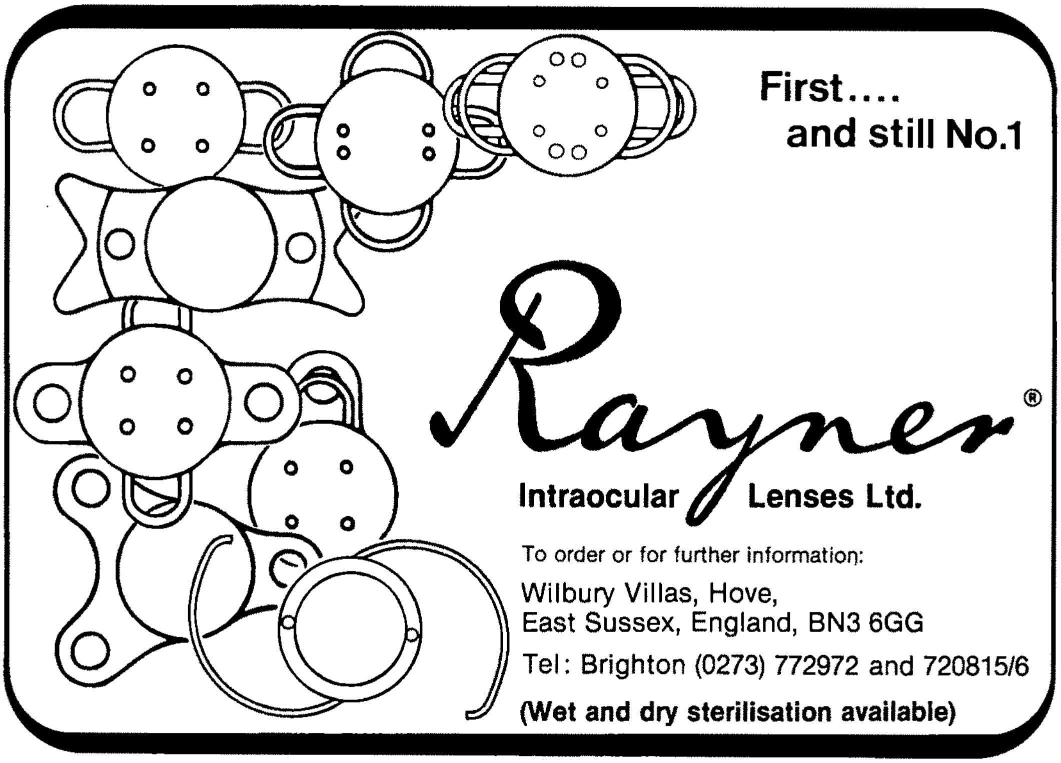

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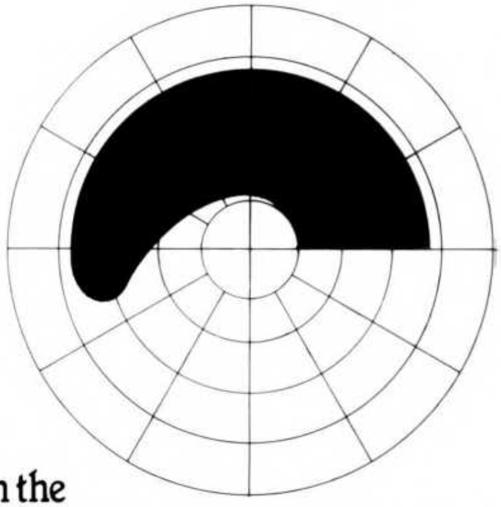

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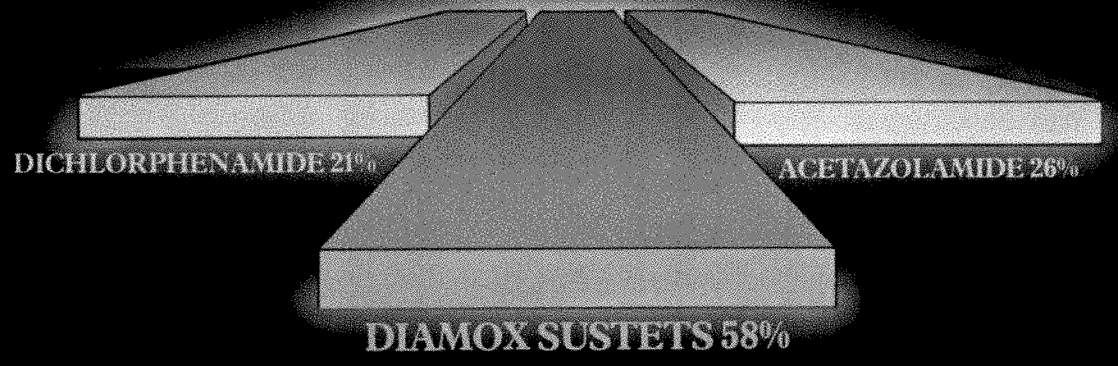

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British Journal of Ophthalmology, 1982, **66**, 77–82

Mechanisms of optic disc swelling with diffuse choroidal melanomas: clinicopathologic correlations

GARY C. BROWN AND JERRY A. SHIELDS

From the Oncology Service, Wills Eye Hospital and Research Institute, Thomas Jefferson University, Philadelphia, USA

SUMMARY The clinical and histopathological findings in the eyes of 2 patients with diffuse malignant melanoma of the choroid are described. The tumours were minimally elevated and nonpigmented in the peripapillary area, and both had an associated nonrhegmatogenous retinal detachment. Extension of the tumour into the region of the lamina choroidalis in each eye appeared to cause a localised constriction of the optic nerve and subsequent swelling of the optic nerve head. In addition tumour infiltration of the nerve head was present in one eye. Ophthalmoscopic, fluorescein angiographic, and ultrasonographic characteristics that differentiate between extensive tumour infiltration of the optic nerve head and swelling secondary to other causes are presented. The importance of appreciating this difference clinically is discussed.

Diffuse choroidal melanomas are relatively rare, comprising less than 5% of all malignant melanomas of the choroid.[1 2] The clinical diagnosis of diffuse choroidal melanoma is often difficult, and in a series reported by Font and associates[1] the correct diagnosis was made preoperatively in only 36% of cases. The diagnostic difficulty results from the fact that such tumours are often flat and relatively nonpigmented, lacking the ophthalmoscopic features of most choroidal melanomas.

Case reports

CASE 1

A 69-year-old white woman presented in December 1978 with a history of recent onset of light flashes and decreased vision in the right eye. Ocular examination disclosed a best corrected visual acuity of 6/30 in the right eye and 6/12 in the left eye. An afferent pupillary defect was present in the right eye. The slit-lamp examination showed normal appearances in each eye and no anterior vitreous cells were noted. Applanation intraocular pressures were 12 mmHg in each eye.

The fundus examination of the right eye showed a swollen optic nerve head with indistinct margins. The retinal blood vessels appeared normal in calibre and configuration. Located immediately inferotemporal to the optic nerve head was a minimally thickened subretinal yellow mass that extended inferiorly, where it became more pigmented and attained a maximum height of about 3 mm. Numerous small orange-brown spots, which appeared to be at the level of the retinal pigment epithelium, were present in the macular area. A shallow nonrhematogenous retinal detachment with shifting subretinal fluid was present over the lesion in the inferior peripheral fundus. The fundus of the left eye was normal. The clinical diagnosis at this time was malignant melanoma of the choroid of the right eye. An incisional ^{32}P test was negative, with 25% greater uptake over the lesion than in the control area.

The patient was observed without treatment until October 1979, when the visual acuity had decreased to counting fingers in the right eye. The nonrhegmatogenous retinal detachment had extended to involve the temporal retina also (Fig. 1), and the optic nerve head was more swollen than it had been 10 months previously.

Intravenous fluorescein angiography (Fig. 2) showed early diffuse hyperfluorescence of the optic disc and mottled areas of hyperfluorescence and hypofluorescence in the peripapillary region. The many small hypofluorescent spots located on the surface of the lesion corresponded to the orange-brown pigment seen clinically.

Contact B-scan ultrasonography of the right eye disclosed an initial echo followed by low internal

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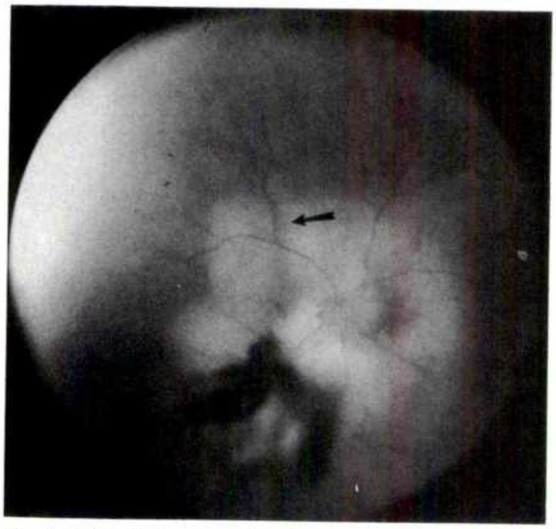

Fig. 1 *Case 1. Equator-plus photograph showing the fundus appearance in October 1979. A predominantly amelanotic choroidal lesion surrounds the optic nerve head and is pigmented inferotemporally. The lesion was diffusely raised to about 1·0 to 1·5 mm, except in the region of the inferotemporal, disc-sized, darkly pigmented nodule, where it measured approximately 3·0 mm in height. The associated nonrhegmatogenous retinal detachment can be seen temporally (arrow).*

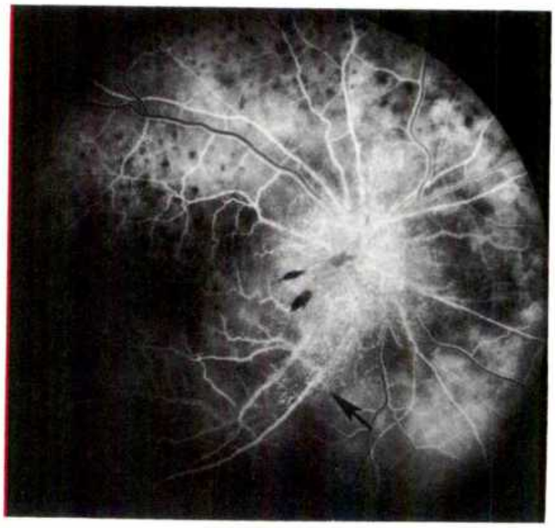

Fig. 2 *Case 1. Laminar venous filling phase 45° fluorescein angiogram of the right eye in October 1979. Many small-vessel telangiectatic changes on the optic nerve head are apparent and these can be seen extending inferotemporally from the optic nerve in the region of distribution of the radial peripapillary arteries (arrow). The optic nerve head was essentially uniformly hyperfluorescent throughout the angiogram. Mottled choroidal hyperfluorescence and hypofluorescence can be seen throughout the field. The 2 hypofluorescent foci located on the temporal portion of the optic nerve head correlate with the haemorrhages seen clinically (Fig. 1), and the many hypofluorescent spots located temporally and superiorly correspond to the orange-brown pigment present on the surface of the tumour.*

reflectivity in the area of the optic nerve head. The A-scan ultrasonogram showed a high initial spike followed by a progressive decrease in echo activity in the area of greatest tumour elevation inferotemporal to the nerve head.

Because of the decreasing visual acuity, increase in subretinal fluid, and increased swelling of the optic nerve head, another cutting ^{32}P test was performed. Uptake over the pigmented region of the tumour was positive at 92% greater than the opposite control quadrant. The eye was subsequently enucleated.

Pathology

Gross examination of the sectioned globe revealed a diffuse tumour, with nonpigmented and pigmented regions, measuring approximately 18×18×1 mm. No evidence of pigmentation was seen on the external sclera or within the vortex veins. Low-power microscopic examination (Figs. 3, 4) disclosed a diffuse tumour replacing the choroid posteriorly. The tumour extended into the region of the optic nerve head and appeared to compress the lamina choroidalis region of the nerve. No direct invasion of the optic nerve head itself was noted. While occasional nests of tumour cells were seen in the vicinity of the meninges, no frank extension into the subarachnoid space could be seen. The optic nerve head was diffusely thickened, and serous subretinal fluid was present inferiorly.

The tumour cells were essentially nonpigmented except in the inferior aspect of the lesion, where pigmentation had been noted ophthalmoscopically. The tumour was composed of plump epithelioid cells with prominent nucleoli and abundant cytoplasm and small areas of spindle B cells. The final diagnosis was diffuse choroidal malignant melanoma of the mixed cell type.

The patient was alive and without evidence of metastatic disease 14 months after enucleation.

CASE 2

A 66-year-old white male was first seen in December 1973, at which time he related a history of painless, progressive visual loss in the left eye over a 4-month period. The patient had otherwise been in good health but did have a 40-year history of cigarette smoking.

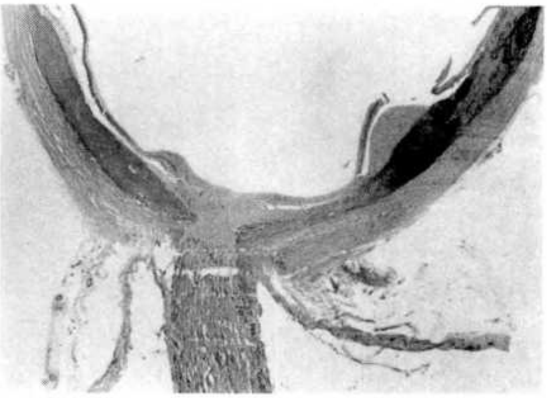

Fig. 3 *Case 1. Posterior aspect of the right globe, showing diffuse infiltration of the tumour throughout the choroid. (Haematoxylin-eosin, original magnification × 1·5).*

Ophthalmological examination disclosed a visual acuity of 6/12 in the right eye and hand motions in the left eye. The applanation tonometry reading in the left eye was 14 mmHg and in the right was 12 mmHg. The slit-lamp examination was normal in each eye and funduscopic examination of the right eye was unremarkable. Ophthalmoscopy of the left fundus revealed a minimally raised, hypopigmented, horseshoe-shaped choroidal mass occupying the posterior pole, and extending temporally and inferiorly. The mass surrounded the swollen optic nerve head (Fig. 5) and involved the total macular area. The nerve head itself was pink superiorly and had a fluffy yellow appearance inferiorly. Shifting subretinal fluid could be seen in all quadrants of the fundus.

Fluorescein angiography of the left eye (Fig. 6) showed early hyperfluorescence of the superior part of the nerve head due to filling of the many dilated surface vessels. The inferior half, that characterised by the fluffy yellow infiltrate, was relatively hypofluorescent during the early phases of the angiogram. Later in the angiogram the total nerve head became hyperfluorescent except in areas where overlying blood was present.

Contact B-scan ultrasonography disclosed the presence of diffuse choroidal thickening, subretinal fluid, and a swollen optic nerve head with moderate to high internal reflectivity.

A thorough systemic examination revealed no other abnormalities, and the patient was thought to have either metastatic carcinoma to the choroid or a diffuse choroidal melanoma. An incisional ^{32}P test was performed and was positive, with the lesion showing 191% greater uptake than the opposite uninvolved control quadrant. The eye was enucleated.

Pathology

Gross sections of the globe revealed diffuse thickening of the choroid, to a maximum of about 1·5 mm, by a minimally pigmented tumour (Fig. 7). The retina was totally detached. Examination of the optic nerve (Fig. 8) disclosed diffuse infiltration by tumour cells extending posterior to the lamina scleralis, but not to the line of surgical excision. A focal dense accumula-

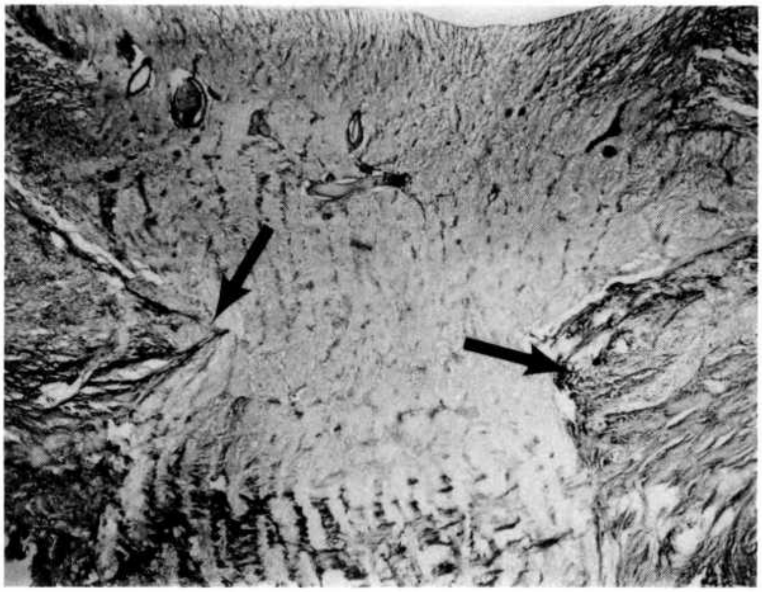

Fig. 4 *Case 1. Low-power photomicrograph of the optic nerve in the right eye. The optic nerve head is swollen but not directly invaded by the choroidal tumour. Tumour can be seen compressing both sides of the optic nerve in the area of the lamina choroidalis. Occasional nests of tumour cells were seen in the region of the meninges, but no direct extension of the tumour into the subarachnoid space was observed. The furthest advance of the melanoma toward the optic nerve is indicated by the arrows. (Haematoxylin-eosin, × 6·7).*

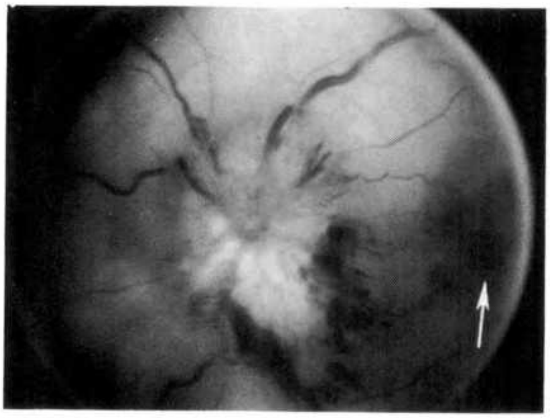

Fig. 5 *Case 2. Left optic nerve head at the time of presentation. The disc is markedly swollen and the inferior half is characterised by a fluffy yellow appearance, while dilated telangiectatic vessels are more readily apparent over the superior half. Blood can be seen along the temporal and inferior borders of the nerve head, and the major retinal veins are dilated and tortuous. The nerve head is completely surrounded by hypopigmented choroidal tumour, though a small amount of pigment (arrow) can be seen in the central macular area.*

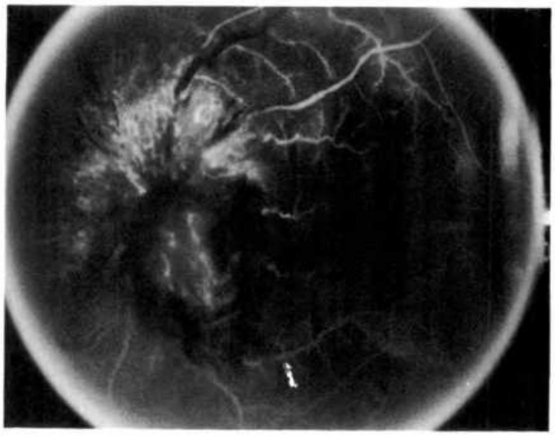

Fig. 6 *Case 2. Fluorescein angiogram of the left fundus in the retinal laminar venous filling phase. The superior half of the nerve head is hyperfluorescent secondary to filling of the many dilated superficial vessels. In comparison the inferior half of the nerve head is hypofluorescent. The markedly hypofluorescent inferior disc borders correspond to areas of superficial haemorrhage (Fig. 5), while the relatively hypofluorescent central inferior disc corresponds to the fluffy yellow infiltrate. Some blood vessels can be seen within this region of yellow tissue.*

tion of these cells was present centrally on the surface of the inferior half of the disc, and this inferior concentration of cells corresponded to the yellow infiltrate seen clinically on the nerve head (Fig. 5). A few scattered cytoid bodies were seen in the peripapillary region, but none were noted overlying the optic nerve head.

The choroid was replaced in the posterior pole by tumour tissue, and compression of the optic nerve by this tissue was evident in the region of the lamina choroidalis. Emissary channels in the sclera as well as periocular soft tissues nasal to the optic nerve were also involved by tumour. Spindle shaped cells with round to oval nuclei and prominent nucleoli were present in addition to areas of epithelioid cells. The histological diagnosis was choroidal melanoma of the mixed cell variety.

The patient died 6 months after enucleation, with diffuse metastatic tumour to the lungs.

Discussion

Font *et al.*[1] have described criteria for the classification of a choroidal melanoma as a diffuse type. Primary choroidal melanomas involving a minimum of one-quarter of the uvea, excluding the iris and ciliary body, and less than 7 mm in height are generally included in this group. The tumours described in this paper are actually less elevated than

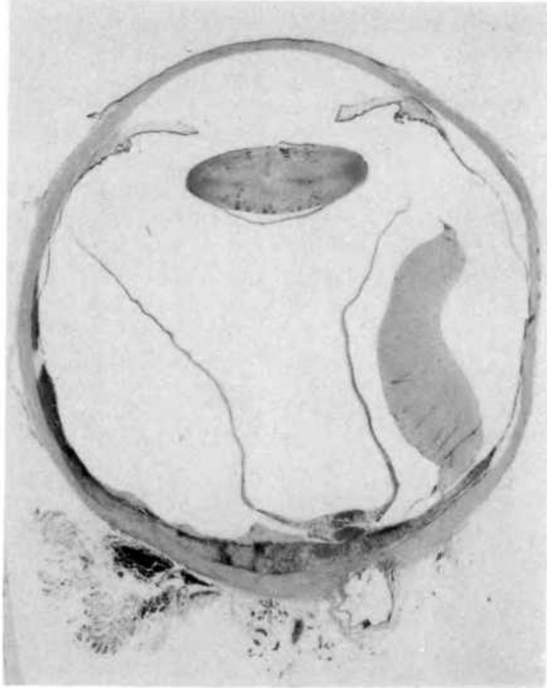

Fig. 7 *Case 2. Gross section of the left globe. The choroid is diffusely infiltrated by minimally pigmented tissue and a serous retinal detachment is evident.*

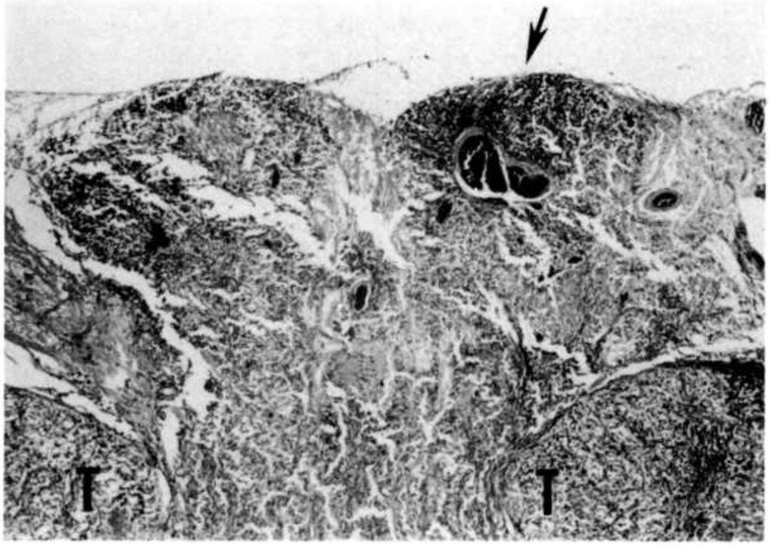

Fig. 8 *Case 2. Low-power microscopic section of the left optic nerve head. Solid tumour (T) can be seen compressing the nerve from both sides in the vicinity of the lamina choroidalis, and the nerve is diffusely infiltrated by tumour cells. A dense accumulation of tumour cells (arrow) can be seen centrally on the surface of the nerve and corresponds to the fluffy yellow material seen clinically (Fig. 5). Blood is present on both sides of this superficial infiltrate, and no cytoid bodies were observed overlying the nerve head.*

many in the above authors' series, for their tumours averaged 3 to 5 mm in thickness.

In contrast to typical choroidal melanomas the clinical diagnosis of diffuse choroidal melanomas is often extremely difficult. From our recent experience and previous reports[2–4] it seems that those entities most likely to be confused with diffuse choroidal melanomas include disciform macular degeneration, metastatic carcinoma to the choroid, choroidal haemangioma, and retinal detachment. Font *et al.*[1] found that the preoperative clinical diagnosis was correct in only 36% of 53 cases, though in another 24% some unspecified introacular tumour was suspected. In the remaining cases (40%) the diagnosis of an intraocular tumour was unsuspected even at the time of enucleation. The difficulty of diagnosis in the past is attested to by the fact that in many eyes symptoms were present for years prior to enucleation.[1 5] The presence of variegated pigmented regions on a raised mass, brown and orange pigment overlying the lesion, and typical ultrasonographic characteristics should arouse suspicion that a diffuse choroidal melanoma may be present. Fluorescein angiography may be helpful by showing areas of mottled hyperfluorescence and hypofluorescence,[6] the latter often corresponding to clumps of macrophages containing lipofuscin pigment,[7] as was the case with our first patient.

The cell type of diffuse choroidal melanomas is variable, though in the largest series described[1] 85% were classified as either mixed cell type, pure epithelioid cell type, or necrotic. When eyes with all types of choroidal melanomas and optic nerve head extension are examined, mixed and epithelioid cell types again constitute nearly 85% of cases.[8]

The 5-year mortality rate following enucleation for diffuse choroidal melanomas is about 73%.[1] The frequent delay in diagnosis, the propensity of these tumours to be exceptionally malignant, and their high incidence of extrascleral extension all account for the high death rate. These tumours may leave the globe locally via the ciliary vessels, ciliary nerves, vortex veins, and leptomeningeal sheaths. In addition orbital extension of any choroidal melanoma which has invaded the optic nerve carries a very poor prognosis for survival,[8 9] as exemplified by the second case.

The optic nerve head swelling in our cases appeared to result from more than one mechanism. A focal constriction of the nerve by surrounding tumour in the area of the lamina choroidalis was present in each case. Possibly a disturbance in axoplasmic transport, with subsequent blockage in the area of the optic nerve head, as has been postulated to occur with papilloedema,[10] may have occurred in these eyes. Hypoxia of the nerve may also have been present secondary to infiltration of the adjacent choroid and impairment of the blood supply to the nerve, and perhaps some angiogenic substance secreted by the tumour might have played a role in producing the dilated, telangiectatic nerve head vessels and swelling.

Histopathologically the second case differed substantially from the first by having invasion of the optic nerve head itself by tumour. The microscopic area of most dense tumour infiltration (Fig. 8) could be correlated ophthalmoscopically with the inferior fluffy yellow region of the swollen nerve head (Fig. 5).

Table 1 *Differentiating features between optic disc swelling without tumour invasion of the optic nerve head and swelling with tumour invasion of the nerve head in eyes with diffuse choroidal melanoma*

	No invasion (case 1)	*Invasion (case 2)*
Ophthalmoscopic appearance of swollen nerve head	Diffusely pink	Fluffy yellow tissue present
Fluorescein angiography of nerve head		
Early	Hyperfluorescence	Hypofluorescence (corresponding to yellow tissue)
Late	Hyperfluorescence	Hyperfluorescence
Ultrasonography of nerve head	Low internal reflectivity	High internal reflectivity

which initially was relatively hypofluorescent with fluorescein angiography (Fig. 6). While this area appeared clinically similar to what is seen with multiple infarctions of the nerve fibre layer, only a few scattered cytoid bodies were seen microscopically in the peripapillary region and none were observed over the nerve head. In the first case the optic nerve head, which was swollen but not infiltrated by tumour, was congruously pink and uniformly hyperfluorescent during the early phases of the angiogram. Ultrasonographically it was noted that the optic nerve head without tumour infiltration showed low internal reflectivity, while that with infiltration showed moderate to high reflectivity. A summary of the differentiating features that help to determine whether tumour invasion of the optic nerve head is present is shown in Table 1.

Thus it appears that ophthalmoscopically, fluorescein angiographically, and ultrasonographically it is possible to differentiate direct tumour invasion of the optic nerve head from nerve head swelling secondary to constriction of the nerve or some other mechanism. This differentiation is important clinically, because tumours which have invaded the optic nerve head are likely to show retrolaminar invasion of the nerve as well, thus necessitating special attempts to obtain a long section of the optic nerve at the time of enucleation.[8]

This study was supported in part by the Retina Research and Development Foundation, Philadelphia, the Ocular Oncology Fund, Wills Eye Hospital, and the Pennsylvania Lions Sight Conservation and Eye Research Foundation, Inc.

The first patient was referred by Drs Morton Seelenfreund and Dennis Freilich and the second was referred by Dr William H. Annesley Jr.

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British Journal of Ophthalmology, 1982, **66**, 83–95

Retinal complications of optic disc drusen

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SUMMARY Following reports by Sanders *et al.* and Wise *et al.* of optic disc drusen associated with retinal bleeding, an additional 19 cases were studied and followed up for 1 to 10 years (average 5 years). Four of them showed haemorrhages at the optic disc and its borders only, but 15 showed extensive retinopathy with macular involvement. In 3 cases retinopathy was serous and not haemorrhagic. Apart from cases in which bleeding was limited to the disc and its immediate vicinity the main clinical features of the syndrome were as follows: (1) the presence of optic disc drusen; (2) extensive retinal haemorrhages; (3) intraretinal extravasation of serum with or without the presence of blood; (4) elevated mounds lifting the retina and causing striae radiating from the mounds towards the macula and beyond; (5) pigmentary disturbance of the macula or a wider area of papillo-macular bundle after the resolution of acute stages which, while often clinically severe, is compatible with recovery of normal or near normal vision. It is proposed that the syndrome be designated the 'optic disc drusen retinopathy.'

The association between optic disc drusen and retinal haemorrhages involving the macula was first described as a clinical syndrome 10 years ago by Sanders, Gay, and Newman.[1 2] Of the 8 cases presented, 3 showed haemorrhages around the optic disc only, as had been described occasionally in the past by several authors, but the remaining 5 showed a new clinical association. In their perusal of the literature Sanders *et al.*[1 2] traced only 9 sporadic references to bleeding associated with the presence of disc drusen, starting with Gifford's report.[3] All these cases were concerned with the bleeding at or in the immediate vicinity of the optic disc, some with vitreous haemorrhage but none with a more extensive retinal or macular involvement.

Henkind, Alterman, and Wise[4] reported 4 cases of retinal haemorrhages associated with drusen, and an additional 4 cases were reported by the same workers 2 years later.[5] Of their 8 cases 5 had retinal involvement while 3 presented with haemorrhages round the optic disc only. Of the 2 cases reported by Brodrick,[6] one was affected by pseudoxanthoma elasticum, a disease typically connected with retinal haemorrhages, and the second case showed disc splinter haemorrhages alone. Of the 6 cases reported by Ostradovec and Vladykova[7] only 3 presented with disc haemorrhages the other 3 showed gross venous abnormalities of the disc and the retina. This brings to 11 the number of cases on record of disc drusen retinopathy and to 19 the number of cases in which only the disc and its immediate vicinity were affected.

Patients and methods

The clinical material we review consists of 19 personal cases collected during the past 10 years. There were 10 males and 9 females. The age of the patients was as follows: 12–25 years, 8 cases; 26–40 years, 3 cases; 41–60 years, 7 cases; over 60 years, 1 case. The mean age was 38·5. The right fundus was involved in 12 cases, the left in 10 cases (3 cases showed bilateral involvement). Follow-up time was between 1 year and 10 years (mean 5 years), but this figure is based on an analysis of 16 patients only; 3 patients for various reasons could not be followed up. The follow-up included a repeated thorough medical, neurological, ophthalmic, and photographic examination, as well as laboratory tests, particularly aimed at the possible existence of immunological, parasitic, and haematological disease. None was demonstrated in any patient. Fluorescein angiography was done in all cases; the presence of drusen was sometimes revealed in the fellow eye only by angiographic evidence. In all cases but one the presence of drusen of the optic disc,

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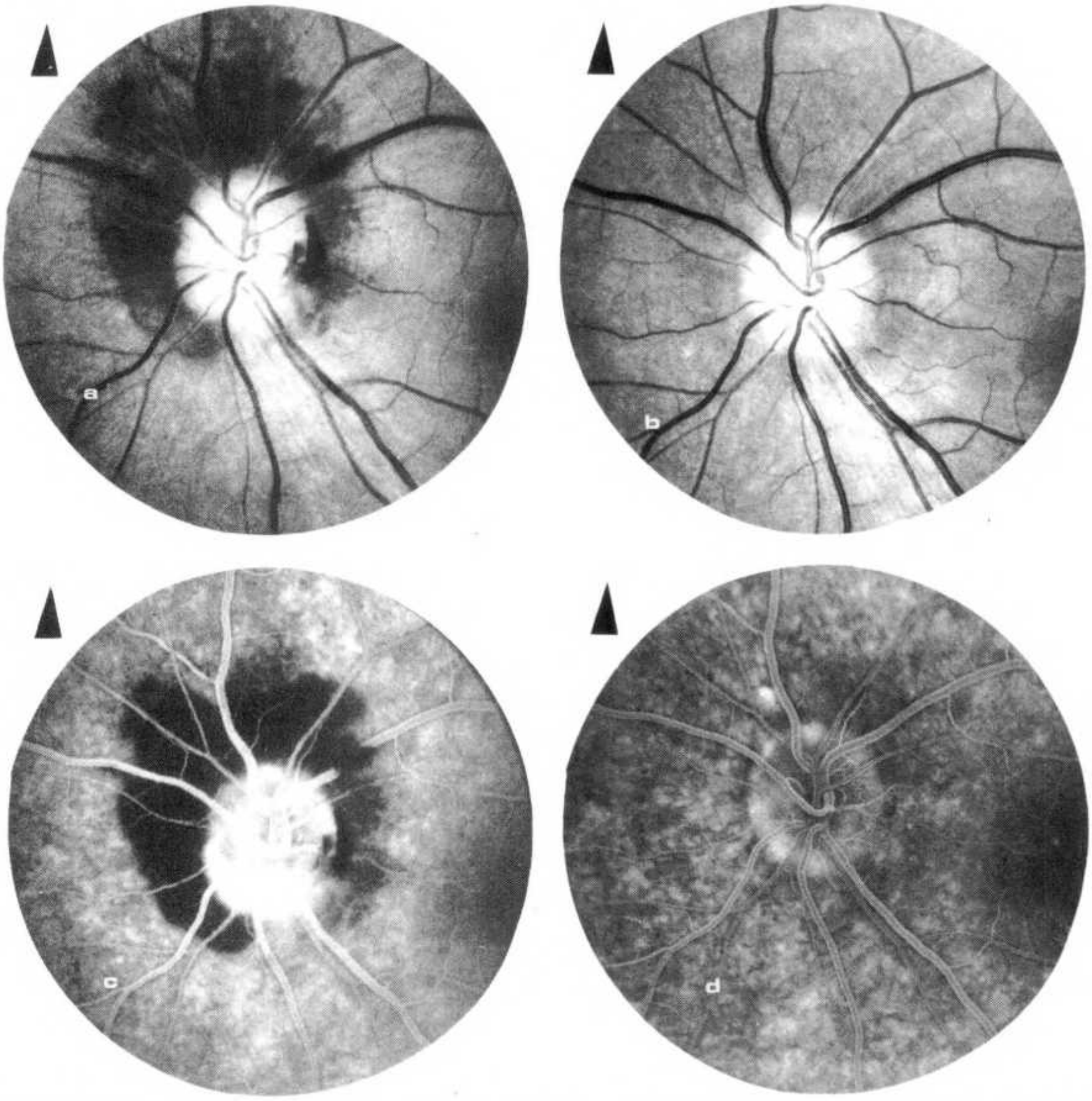

Fig. 1 *Case 1.* (a) *Fundus at first attendance.* (b) *Six months later.* (c) *Fluorescein angiogram at first attendance.* (d) *Six months later.*

buried or adjoining, was demonstrated in the fellow eye.

In 4 cases the optic disc alone and its immediate vicinity were affected by haemorrhages. In the other 15 cases extensive retinal involvement was present.

According to the clinical manifestations at the time of first attendance the cases will be described in the following order: group I, 4 cases (1–4), where only the disc and its immediate vicinity were affected by haemorrhages (Fig. 1); group II, 9 cases (5–13), where the retina was dissected by haemorrhages extending from the optic disc (Figs. 2, 3, 4, 5, 6); group III, 3 cases (14–16), where the retina was dissected by serum dextravasation (without erythrocytes) extending from the optic disc towards the macula (Fig. 7); and group IV, 3 cases (17–19), where a late burnt-out clinical picture was seen with pigment disturbance and scarring of the retina (Figs. 8 and 9). All affected eyes showed disc drusen of various shapes and locations.

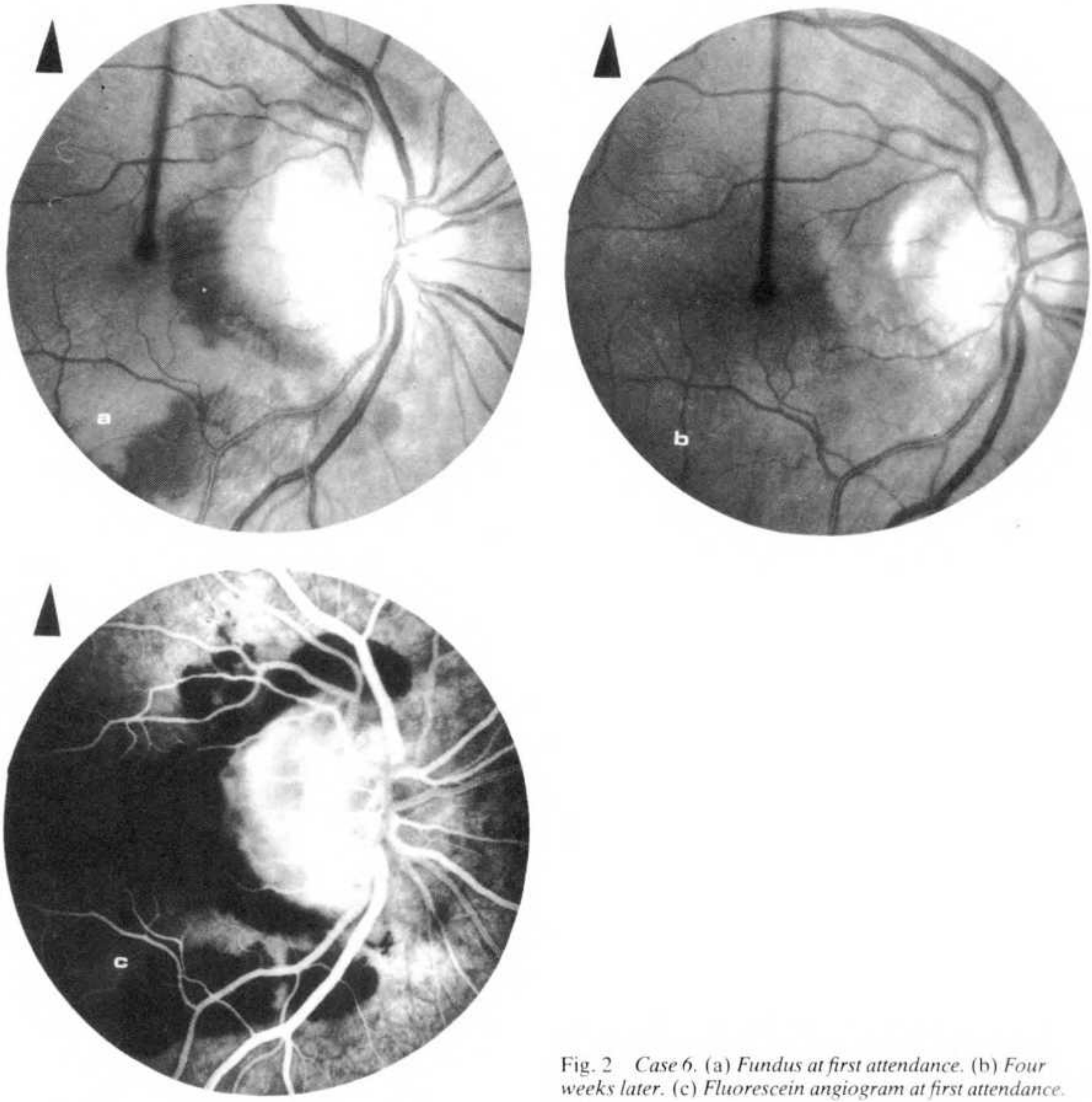

Fig. 2 *Case 6.* (a) *Fundus at first attendance.* (b) *Four weeks later.* (c) *Fluorescein angiogram at first attendance.*

Case reports

CASE 1

A 25-year-old man, an insurance representative, was first seen in June 1973. Nine days previously he noticed some blurring of vision in the left eye, 2 days later a floater was noticed too. His visual acuity was 6/5 each eye. His left eye showed a radiating halo of 'deep' haemorrhage around a swollen disc with a beady crescent of fresh looking blood at its temporal edge. Red-free photography located all these haemorrhages in front of the pigment epithelium and some even in front of retinal vessels. Fluorescein angiography showed lumpy staining of the optic disc. During the following 3 months the vivid marginal blood disappeared and the main haemorrhagic halo faded. Two months later all haemorrhages were gone. When examined last in 1981 (8 years follow-up) the disc looked flat but without physiological cupping. There were no further episodes of blurred vision, which was 6/5 each eye (Fig. 1).

CASE 2

A 48-year-old engineer was examined in February 1977 by an optician who tested him for reading glasses. Visual acuity was 6/5 each eye and there were no symptoms. The left optic disc had a hazy outline and seemed large. At the 12 o'clock meridian there was a fine meshwork of just visible vessels and a small haemorrhage at the edge of the disc on the 3 o'clock meridian. Four months later a string-like horizontal haemorrhage was seen across the nasal half of the disc, and a second round, dark haemorrhage was present at the 6 o'clock meridian. Vision was not affected. Six months later only the deep, round haemorrhage below the disc was present. Red-free photography placed this haemorrhage in front of the pigment epithelium. Six months later no haemorrhages were present. The disc outline was deformed by drusen, but its margins were now clearly defined. The fundus remained unchanged until 1980, when the patient was last seen.

CASE 3

A 55-year-old man was first seen in October 1973 complaining of gradual loss of clear vision in the left eye for the previous 2 months. He could see 6/18 with this eye; the other eye could see 6/9 (corrected). Both eyes showed high mixed astigmatism. The fundi showed swollen optic discs and abnormal, crowded vessel entry. Both fundi showed extensive drusen in the vicinity of but not in contact with the optic disc. The left disc showed a small haemorrhage at its nasal side. Neurological examination proved negative and remained negative for all 8 years of observation. In June 1974 the fundus showed a 'deep' haemorrhage all round the disc, especially vivid at its temporal margin. Vision was unchanged. In August 1974 the haemorrhages were remarkably diminished and in December quite gone. Eight months later a deep diffuse haemorrhage recurred at the temporal margin of the disc. The right disc now also showed a deep marginal haemorrhage at its temporal margin, and fluorescein angiography showed profuse leakage of the dye towards the macula. In March 1976 there was still a rim of haemorrhage in the same location, while the originally affected left eye showed no haemorrhages. In October 1977 both discs were free of haemorrhages and looked much flatter. Both showed limited fluorescein leakage towards the macula. Thereafter, up to 1981, there were no haemorrhages. Visual acuity was 6/12 right eye, 6/18 left eye. Both discs were clearly defined.

CASE 4

A 34-year-old man was seen in 1959. He was neurologically diagnosed as suffering from tuberous sclerosis. His face showed marked sebaceous adenoma. The vitreous of his left eye showed a small globule of an astrocytoma and an optic disc distorted and obliterated by a large, scaly, sharp-edged conglomeration of drusen. At the lower edge of this drusen mound retinal haemorrhages were present.

CASE 5

A 42-year-old typist was seen first in April 1971 with a complaint of failing sight in the left eye for the previous 2 months and a distortion of central vision for the previous week. Vision was 6/18 with this eye and 6/5 with the other. The left fundus showed a somewhat disfigured optic disc clearly affected by buried drusen. About half way towards the macula there was a wide crescent of retinal haemorrhage, and splashes of small haemorrhages were seen along the lower temporal vessels. Red-free photography showed all these haemorrhages to be intraretinal in front of the pigment epithelium. Fluorescein angiography showed early glow from the marginal disc drusen, expanding to engulf the optic disc and towards the macula in the early venous stage. During the following 4 months all haemorrhages were absorbed, but a dark crescentic new haemorrhage appeared close to the lower temporal quadrant of the disc. Visual acuity was 6/12. This took 18 months to absorb, with vision improved to 6/6. When last seen in 1981—10 years after the onset—the optic disc looked flat, and on its temporal side was a round disc-sized area of fine thinning of the pigment epithelium. Between the two, at the disc edge, was a sharp splinter of black pigment. The macula seemed normal. Vision was 6/5 each eye.

CASE 6

A woman part-time cleaner aged 25 was first seen in April 1980 when she complained of light flashes to the right of the fixation point and a hazy film affecting the right eye for the previous few days. Her vision was 6/5 each eye. The right fundus showed a large, grey swollen drusen body at the upper temporal edge of the disc and extensive retinal haemorrhages between the disc and the macula. Fluorescein angiography showed a strong, early glow of the disc extending towards the macula. Four weeks later all haemorrhages were gone, as were her symptoms. A glistening, yellowish, elevated crescent of drusen remained at the upper temporal edge of the disc. The macula showed fine pigment stippling. The eye remained unchanged for the remaining 12 months of follow-up (Fig. 2).

CASE 7

A 12-year-old schoolboy was first seen in August 1971 complaining of blurred vision in the left eye. Vision was 6/36 with this eye and 6/5 with the other. The left optic disc was fringed temporally by a whitish, elevated drusen body which showed a crescent of haemorrhage convex towards the macula. Striate oedema streamed from the drusen body

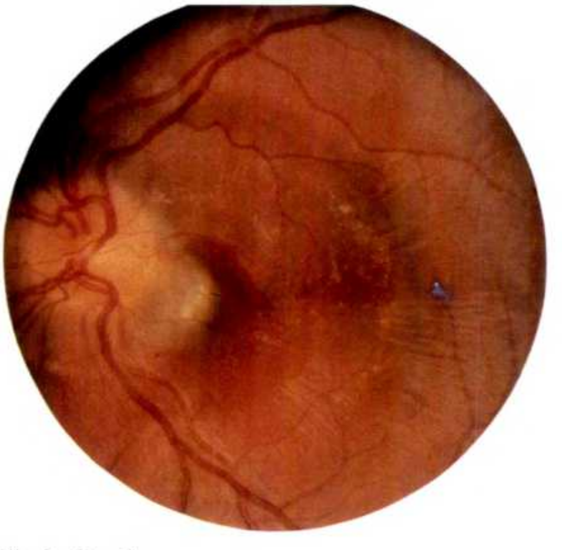

Fig. 3 *Case 7.*

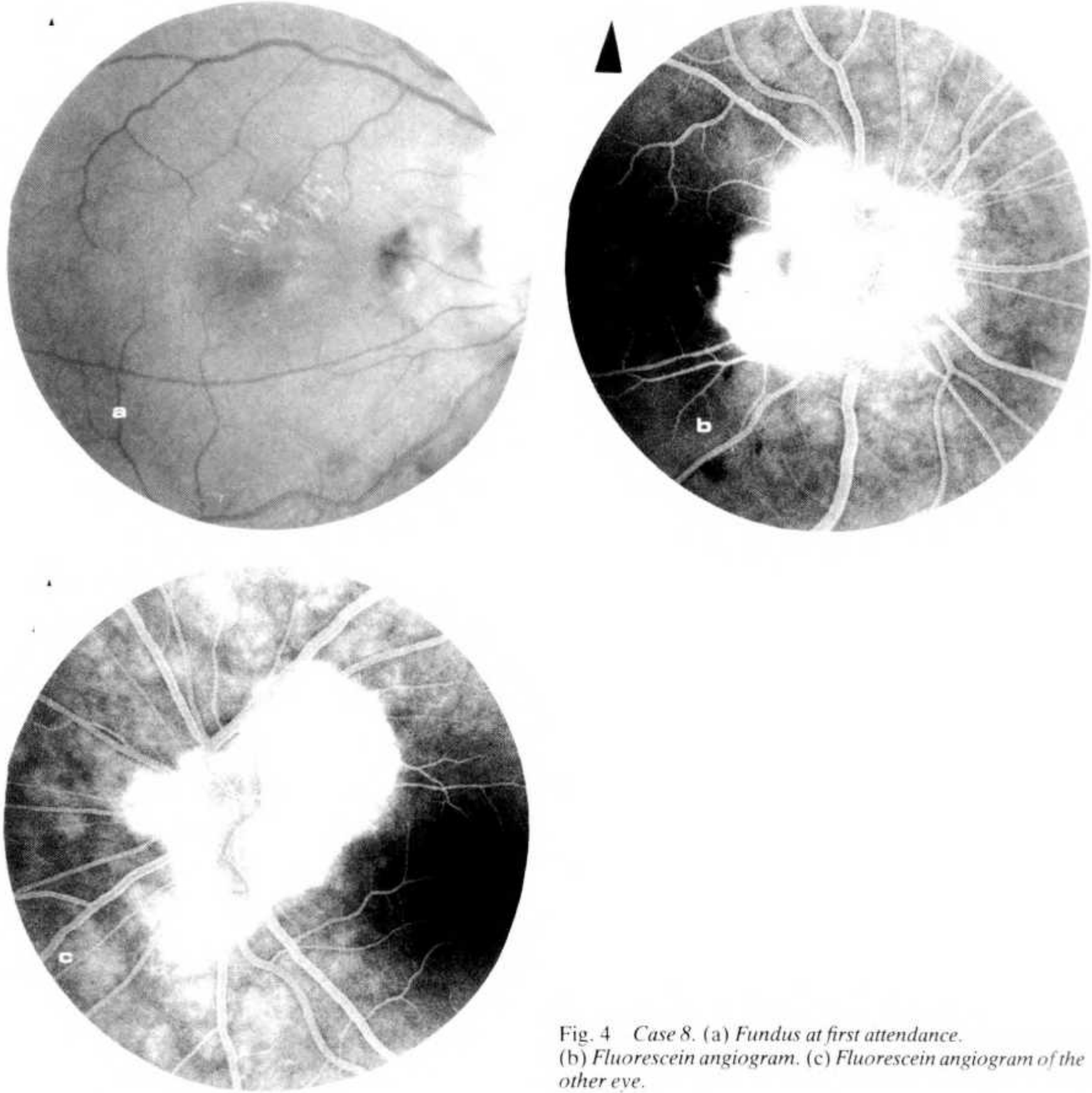

Fig. 4 *Case 8.* (a) *Fundus at first attendance.* (b) *Fluorescein angiogram.* (c) *Fluorescein angiogram of the other eye.*

toward and across the macula, which was spattered by subneuroepithelial deposits. Two months later vision was 6/12 and the fundus was free of haze. The disc adjacent to the drusen body was better defined and smaller. Some neuroepithelial detachment with posterior yellow dusty deposits persisted. Fluorescein angiography showed late but increasing staining of the drusen body but not of the disc. Five months later visual acuity was 6/9. Three years later (1975) vision was 6/12. The macula showed pigmentary disturbance. The drusen body was oval, white, with black granular deposits, and seemed separated from the disc. The patient then moved away, but to our recent inquiry (1981) replied that he had had no further trouble with his eyes and that he could see well (Fig. 3).

CASE 8

A 52-year-old housewife was first seen in March 1976. She noticed gradual deterioration of vision in the right eye for the previous 3 months. Her vision was 6/36 in this eye and 6/4 in the other. The fundus showed the optic disc to be deformed by multiple buried drusen. Close to the large drusen located in the temporal area of the disc, but separated from it, there was a slaty, small lump of pigment. There were a few small retinal haemorrhages within the lower half of the arcuate vessel area. The macula showed a round swelling of serous detachment with a cluster of brush-like white exudates in the nerve fibre layer and some depigmentation. Red-free photography showed the peripheral haemorrhages to be intraretinal but the slaty mound near the disc subretinal. Fluorescein angiography showed a strong penetration of the dye from the glowing disc towards the macula, and several drusen round the disc margins which were not seen ophthalmoscopically. There were no recurrences during the following 5 years. The slaty mound became a whitish thin scar with scattered pigment dots; the macula now showed extensive pigment scatter and depigmentation. Vision returned to 6/12.

The other eye showed—from her first attendance—exuberant multiple small drusen of the optic disc, distorting its outline, particularly along the superior temporal vessels, where a prominent separate drusen body was placed far from the normal disc territory and bordered nasally by a small haemorrhage. Fluorescein angiography showed a diffuse pooling of the dye over all this area and the disc. When it was seen 5 years later (1981) there was a marked increase in size and number of these drusen. Her visual acuity was 6/6 (Fig. 4).

CASE 9

A healthy girl of 23 was first seen in February 1976 complaining of distortion of vision in her right eye, which had started 2 months previously. During the previous 4 weeks the distortion disappeared and her vision became very poor, but it had been improving since then gradually. Visual acuity was 6/12 with this eye and 6/4 with the other. The right fundus showed a pink disc with filled physiological cupping. At its temporal side there was an elevated crescentic roll of greyish colour, a small intraretinal haemorrhage bordered it inferiorly, and another small haemorrhage was seen nearer to the macula. The macula was elevated by a disc-sized serous detachment with a sprinkling of flecked, dust-like, yellow deposits, and retinal striae ran across it from the disc drusen towards the periphery. Fluorescein angiography showed intensive glow of the drusen body, which involved even in later stages only the temporal part of the disc. It spread, however, towards the macula and along the superior temporal arcuate vessels. For the next 3 months there was a gradual drying of the fundus and vision improved to 6/9. When seen in 1981—5 years after onset—visual acuity was 6/5; the macula showed a very delicate stippling only. The disc drusen body was shrunk, with patchy dense pigmentation (Fig. 5).

CASE 10

A 60-year-old postal supervisor was first seen in April 1978. Two months previously he noticed a dense shadow in the right eye, which since then decreased in size. His vision was 6/24 in this eye; vision in the other eye was 6/6 and was normal. The right fundus showed blurred disc margins with 3 small satellite drusen and an intraretinal sheet of haemorrhage extending from the temporal disc margin towards the macula. The macula showed cystic degeneration. Fluorescein angiography showed a strong glow of the disc and the main drusen, extending towards the macula along the superior arcuate blood vessels. During the following months the haemorrhages were gradually absorbed without trace and vision improved to 6/12. Three years after the onset a small whitish linear scar was seen at the 10 o'clock meridian of the disc; the vision remained 6/12 in spite of marked pigment disturbance at the macula.

CASE 11

A 30-year-old window cleaner was first seen in November 1971 complaining of gradual loss of vision in the left eye for the previous month. It was 1/60 in this eye; vision in the other eye was 6/4. A wreath of retinal haemorrhages round the disc extended from the 10 o'clock radius to the 6 o'clock meridian. The centre of this wreath was deeply oedematous. From this swollen centre some striae stretched over the macula. Fluorescein angiography showed copious infusion of the dye into the area, extending towards the macula. Marked disturbance of the pigment epithelium affected the oedematous central area. The equatorial periphery of either eye showed many small yellowish spots which stained with fluorescence. Within 4 weeks there was considerable absorption of haemorrhages and flattening of the central oedema. A large drusen body at the temporal half of the disc came to light. All clinical investigations, particularly those concerned with parasitic infection, proved negative. During the following year there was only slow absorption of retinal haemorrhages and striae, very incomplete at the patient's last attendance. His vision never improved, but the affected eye showed hypermetropic astigmatism—the right eye was emmetropic—and a large central scotoma in the affected eye could have been suppressive. The patient was followed up for 12 months only, when he emigrated overseas.

CASE 12

A 25-year-old waitress was first seen in February 1976 with a history of an attack of blurred vision of the right eye 6 months ago, lasting for a few weeks. The sight in her left eye became blurred again 4 months later but 2 weeks before attending here showed much improvement. Vision was actually 6/5 in each eye when examined. Both fundi showed a disfigured optic disc outline and clumpy pigmentation at the maculae. Four weeks later sight in the left eye became blurred, down to 6/36. Fluorescein angiography showed early strong glow of the optic disc and stippled pigment disturbance between the disc and the macula, which eventually was engulfed from the disc effusion, and this progressed temporally to form a glowing ring round the macula. A few small haemorrhages were seen near the temporal disc edge. The vision in the left eye became 6/5 within 4 weeks, but 3 months later the vision of the right eye failed to 2/60. There was an extensive oedema of the posterior pole of the eye but no haemorrhages. Two weeks later visual acuity improved to 6/9, but vision in the left eye dropped to 5/60, and the fundus showed similar extensive oedema of the posterior pole. During the next 2 months the vision of both eyes improved to 6/5 and in the following 2 months to 6/4. Both fundi showed delicate pigment clumping at the maculae, and in the right eye a large triangular scar was present temporally to the macular area over the previous limit of oedema. There was no change in the fundi in the following 4 years.

In June 1980, however, the patient returned complaining of blurred vision in the left eye. The visual acuity was 6/5 in each eye, but on the nasal side of the left eye a prominent marginal drusen body was surrounded by a sheet-like retinal haemorrhage extending nasally. Fluorescein angiography showed massive fluorescence of the whole optic disc. In 3 months all haemorrhages disappeared. There was a marked increase in elevation of a drusen body at the 11 o'clock

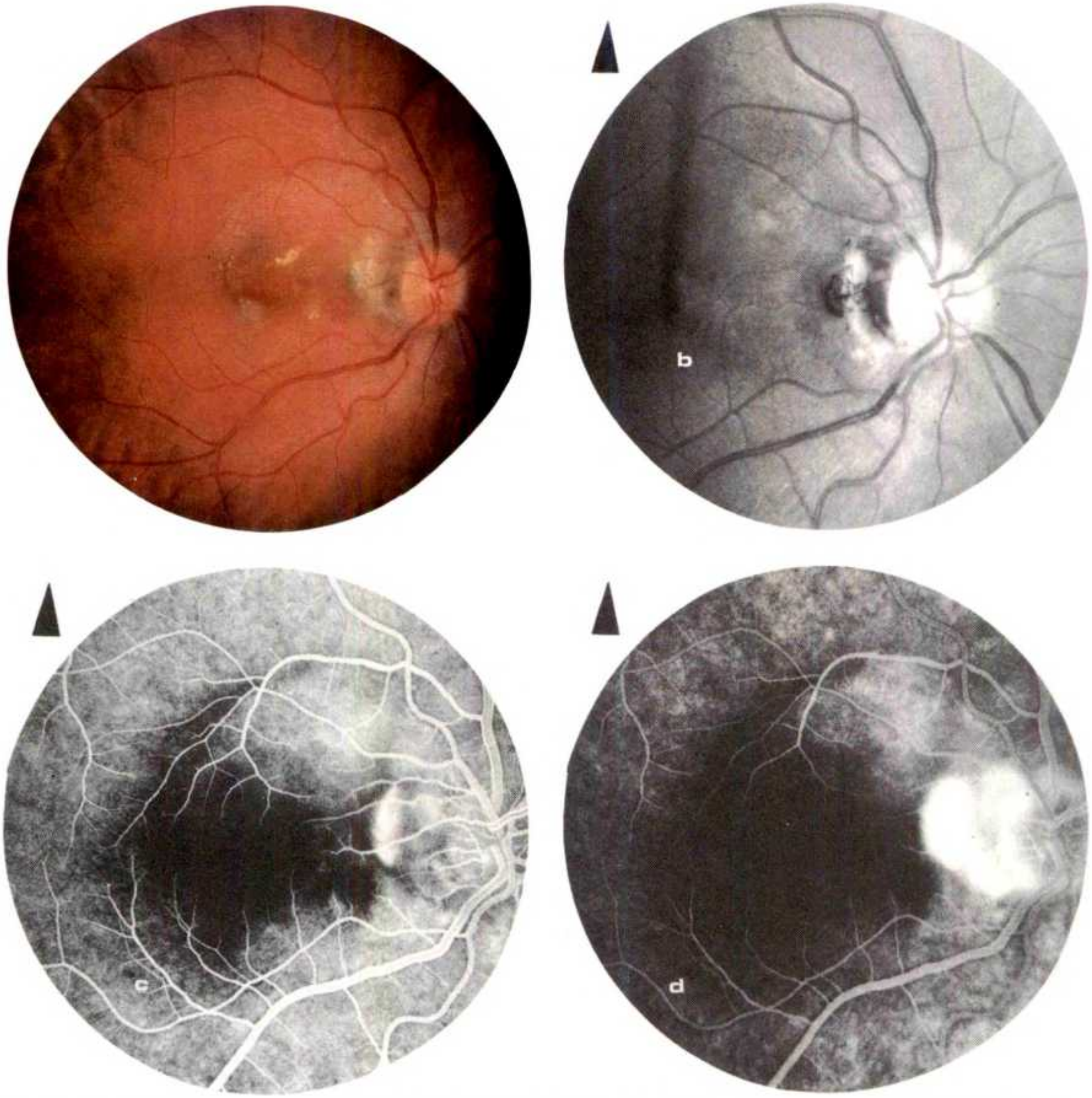

Fig. 5 *Case 9.* (a) *Fundus at first attendance.* (b) *Five years later.* (c) *Fluorescein angiogram at first attendance, early stage.* (d) *Later stage.*

meridian, and new drusen appeared at the lower nasal edge of the disc. The visual acuity of the left eye dropped to 6/6 (5 years' follow-up).

CASE 13

A 16-year-old girl in the 5th month of pregnancy was first seen in January 1976 complaining of loss of sight in the left eye for the previous 4 weeks. She could only count fingers with this eye; vision in the other eye was 6/4. The fundus showed an optic disc without clear margins and deep central white cupping. Its temporal edge was peaked towards the macula and showed strands of pigmentation. At the 3 o'clock meridian a square pigmented mound was seen and a separate plum coloured globule of blood nearly touching the macula, which showed a small, separate haemorrhage and oedema. Fluorescein angiography showed a strong progressive stain from the disc towards the macula. The fundus periphery and equator showed numerous spots characteristic of histoplasmosis, some with a pigmented core and some yellow and unpigmented. The other eye showed the same kind of peripheral spots and a similar disc, but no bleeding or pigment disturbance. During the following 2 years the

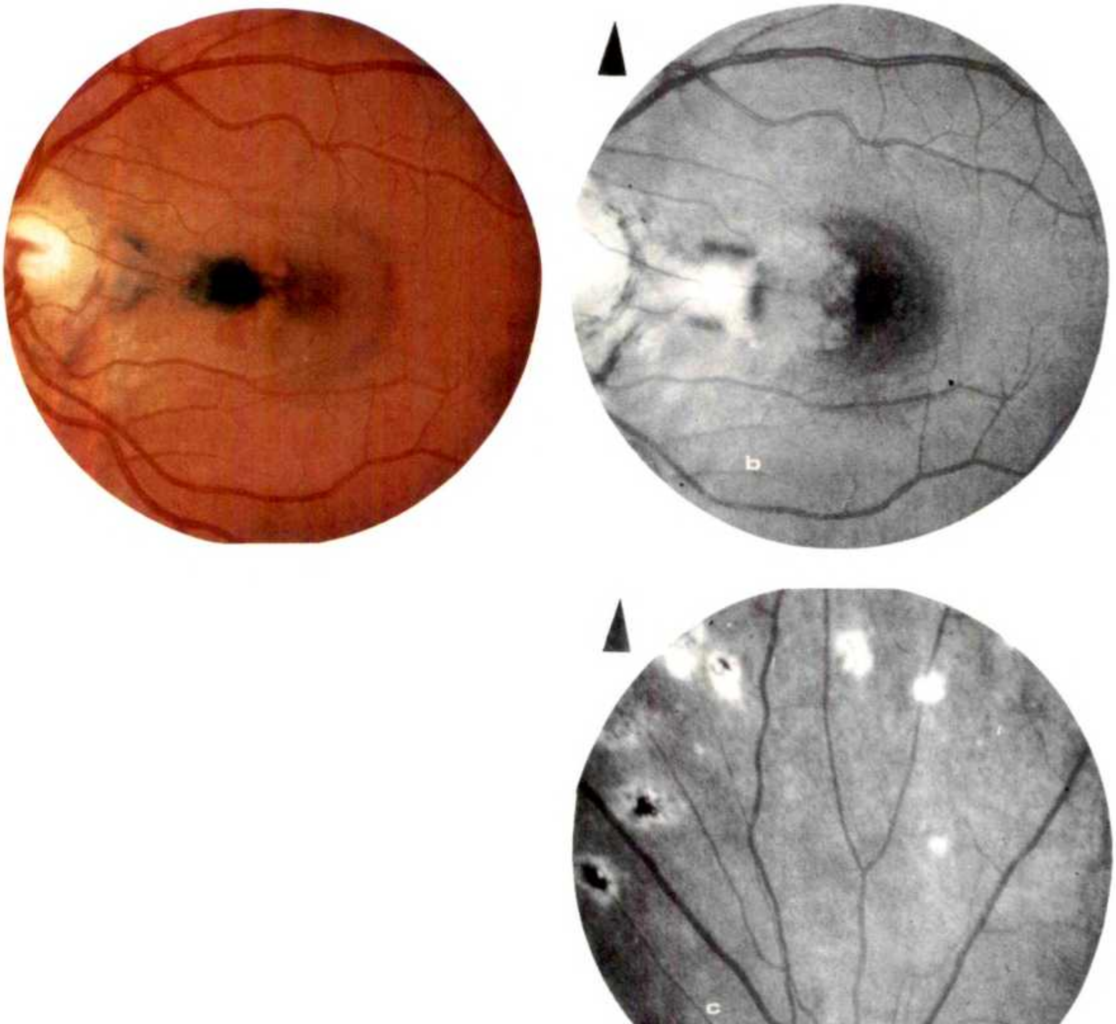

Fig. 6 *Case 13.* (a) *Fundus at first attendance.* (b) *Two years later.* (c) *Peripheral 'histoplasma' spots.*

vision slowly improved to 6/18 and the areas of pigmentation became much lighter in colour. In particular the paramacular mound changed its shape into a doughnut-like pigmented ring with a red centre. This slowly became white, and the ring became broken up into small pigment clumps showing against the white background. The 'histoplasma' spots never changed. Extensive and repeated laboratory investigation, particularly for parasitic infection, were negative (Fig. 6).

CASE 14

A 47-year-old electrician was first seen in December 1975 complaining of blurred vision in the right eye for the past 3–4 months, vision was 6/9 in this eye and 6/5 in the other. The fundus showed an optic disc with softly defined edges and no physiological cupping. Above and temporally a little distance from the disc edge there was an isolated, sharply defined, small whitish drusen body. The central retina and vicinity of this drusen body showed a dusting of the posterior retinal layer with numerous yellowish spots. Fluorescein angiography showed buried drusen distorting the outline of the disc as they took the dye. Only in one direction was there an expansion of the disc glow, temporally towards the macula. When the patient was last seen in 1981—6 years after onset—vision was 6/5 with each eye. The isolated drusen body was only marginally smaller and sharper in outline. Punctate yellowish dust could still be seen in the macular area (Fig. 7).

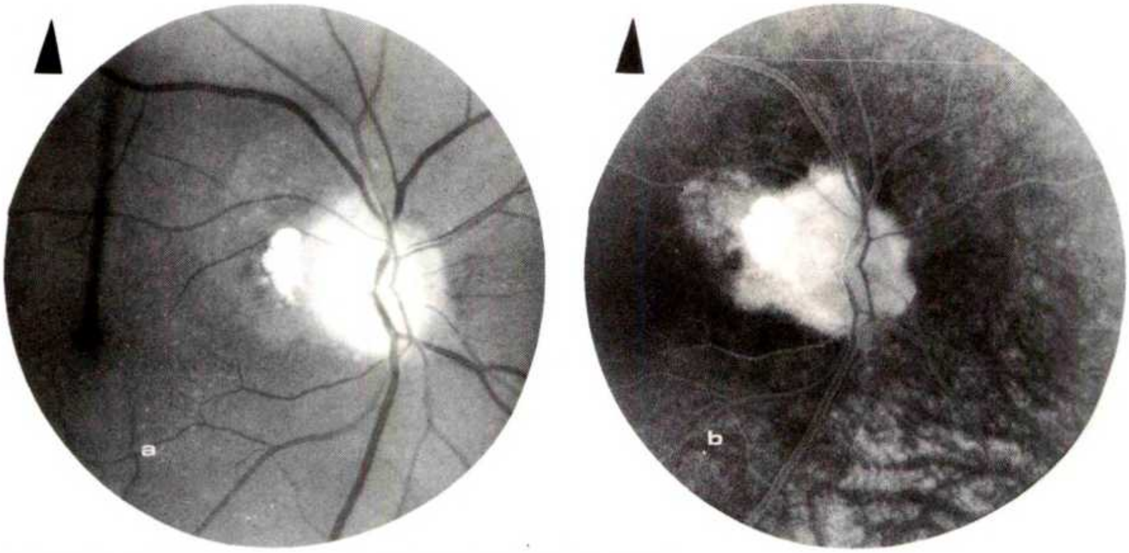

Fig. 7 *Case 14.* (a) *Fundus at first attendance.* (b) *Fluorescein angiogram.*

CASE 15

A 33-year-old housewife was first seen in April 1975 with a 2-week history of disturbance of the upper visual field of the left eye. On examination her vision was 6/6 in this eye; the other eye 6/5, but there was some oedema of the macula. Her symptoms disappeared during the following 6 weeks. In July 1976 she reported back as an emergency because of loss of sight, again in the left eye, which on examination could see 6/24 part. The optic disc showed marginal drusen along its temporal margin, and fluorescein angiography showed a signet-like extension of optic disc glow towards the macula. The vision returned to 6/5 in 4 weeks. In January 1977 she again returned complaining of blurred vision of this eye, and its vision was 6/9 only, while the right eye could see 6/5. A similar picture was seen with the ophthalmoscope and by fluorescein angiography as that seen previously. The condition settled within a few weeks, and when examined last in December 1980 she could see 6/6 right eye, 6/5 left eye. Apart from distortion of the optic disc margin there were no traces of past episodes.

CASE 16

A 67-year-old retired man was first seen in November 1976. Four months previously he noticed blurred vision in the right eye, which after a while started clearing. Vision in the right eye was 6/9, in the left 6/5. The right fundus showed a somewhat elevated whitish crescent at the temporal edge of the disc which showed no physiological cupping. A widespread, delicate stippling of the retina of the posterior pole was noted. Fluorescein angiography showed early glow at the temporal edge of the disc, extending signet-like towards the macula. When he was seen last in 1981—4 years' follow-up—both eyes could see 6/5. The right macula showed fine stippling.

CASE 17

A 62-year-old man, first seen in February 1976, was referred from an optician to whom he went for a replacement of reading glasses. His vision was 6/6 right eye and 6/9 left eye. There was no history of any previous eye trouble. The discs were pink and showed multiple marginal drusen. The macular areas showed irregular scarring of pigment dystrophy bridging from the temporal disc margins towards the maculae. The picture was practically identical in each eye. Fluorescein angiography showed large irregular areas of pigment dispersal within the papillomacular bundle, with pigment scattering reaching from the disc to the macula. Drusen were clearly outlined all round the discs. The

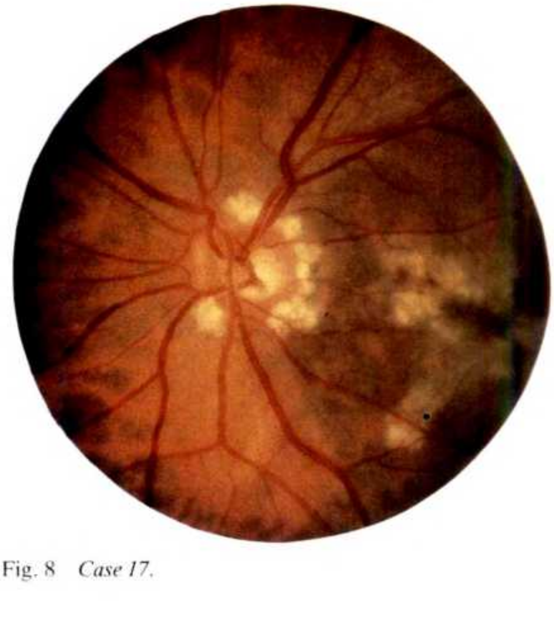

Fig. 8 *Case 17.*

macular function was retained at 6/6, 6/9 vision level for the following 5 years of observation (Fig. 8).

CASE 18

A 17-year-old girl attended an endocrinological clinic in her childhood because of a suspicion of retarded growth, and the idea was entertained that she might be suffering from a tumour of the upper brain stem. All investigations including a CT scan were negative, and no endocrine symptoms were discovered over more than 10 years of neurological follow-up. It was only in 1980 that, because of complaints of headaches, she was again seen by neurologists, and an abnormality of her right fundus was noticed; the disc was suspected of showing oedema. Electrodiagnostic tests and the electroretinogram were all negative, and her visual fields were full. On ophthalmic examination the patient's visual acuity was found to be 6/24 right eye, 6/9 left eye. The right fundus showed marked distortion and drusen of the optic disc, a granular track of pigment dispersion between the disc and the macula, and atrophic spotty and patterned macular dystrophy. The left fundus showed a small disc surrounded by dark crescents and feathery outline, typical of drusen, which were confirmed by fluorescein angiography. It showed a normal macula. The picture is interpreted as a quiescent, late manifestation of drusen of the optic disc connected with haemorrhagic or serous infiltration of the retina.

CASE 19

A 53-year-old man was seen in 1977 after an abnormality of the right fundus was noticed by an optician. His vision was 6/9 in right eye, 6/5 in the left. The fundus showed buried drusen of the optic disc and pigment clumping area from the disc towards the macula, which was involved. Fluorescein angiography showed strong fluorescence of the disc, extending some distance towards the macula signet-like. An area of depigmentation was seen near and below the disc edge. The other disc showed buried drusen but a normal macula (Fig. 9).

Comments on case reports

GROUP I

The 4 cases in this group showed haemorrhages of the optic disc and its immediate vicinity only. Case 4 was seen only once by consultation. His clinical notes were lost, and only the photographic evidence of his adenoma sebaceum and intraocular features of tuberous sclerosis were preserved. The fundus is similar to that described by Gifford,[3] but no mention of an underlying general disease was mentioned in that report. The other 3 cases had very slight symptoms or no symptoms at all, with visual acuity 6/5 in cases 1 and 2, 6/9 in case 3. They had recurrences, case 3 for 3 years, each eye being affected at different times, and recovering within 8–12 months each time. In no case did the blood break through the internal limiting membrane into the vitreous, as described by others, and in no case was the sight permanently diminished by the episodes.

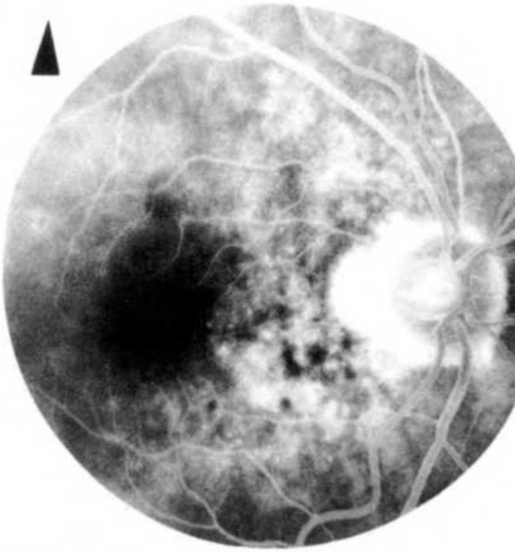

Fig. 9 *Case 19.*

Extensive neurological investigations were all negative, and within a follow-up time of 8 years in 2 cases, and 4 years in the third, no general health problems arose.

The haemorrhages in these patients look darker and they were considered to be 'deep.'[4,5] This is an optical illusion. By the use of the slit-lamp and red-free filters for observation and photography they can be proved to be superficial, in the nerve fibre layer or intraretinal. In our case 1 some were demonstrated in front of the retinal vessels but still behind the internal limiting membrane (Fig. 1).

GROUP II

Nine cases in this group (5–13) constitute the classical symptomatic haemorrhagic retinopathy with macular involvement. Apart from 2 patients who attended within a week because of flashes of light and some distortion of vision, most patients attended with a history of 2–4 months' deterioration of sight, which at this stage varied between 1/60 and 6/5 (average 6/18). Apart from the patient with 1/60 vision, of the other 8 cases 5 recovered their sight to 6/5 level and none to worse than 6/18. The visual recovery was usually parallel with the absorption of haemorrhages. The absorption was complete in 3–4 months, and this applied to recurrences as well, of which there were 1 in case 5, 5 in case 12, and 3 in case 15.

Case 5 was particularly interesting because, while the original fundus picture was classical for this group, with bright red extensive haemorrhages, the recurrence 4 months after the first attack took the shape of a 'deep' disc margin bleeding only—similar to the group I pattern—and this took all of 18 months to be absorbed without disturbing the recovery of visual acuity, in contrast with a few months' absorption of haemorrhages in other patients in this group.

Case 12 was also interesting. While the left eye was originally affected—with a recurrence—by a serous extravasation only, the last attack took the shape of classical sheath haemorrhages. Until that event the diagnosis was very tentative. Case 12, with cases 11 and 13, merits special notice. These 3 cases showed peripheral foci of choroidal scarring—'histoplasma' spots—and case 12 was observed to develop scarred areas through stages of localised oedema. All investigations, particularly aiming at parasitic infection, were negative. 'Histoplasma' spots in the affected eye (case 7) were described by Wise *et al.*[5] It may be of interest to note that the average age of these patients with additional 'histoplasma' changes was distinctly lower than overall, 23·5 as opposed to 38·5 (Figs. 2–6).

GROUP III

In cases 14, 15, and 16 the intraretinal extravasation was serous and not haemorrhagic. Case 12 combined both. All patients in this group attended with complaints of blurred vision for the previous 1 to 4 months, and the recovery took a few months, just as in the cases of group II. Case 15 had 2 recurrences; the visual impairment was 6/9 (recovering to 6/5), 6/24 (recovering to 6/5), and 6/9 (recovering to 6/5). At the macula, or in a more extensive papillomacular bundle area, signs of schisis were present, with dusting by white specks of posterior retinal lamina. In all cases fluorescein angiography showed a characteristic signet-like stain of the disc with its drusen extending towards the macula.

The mean age of the patients was 49, considerably higher than overall for the other groups (Fig. 7).

GROUP IV

Three patients in this group were 17, 53, and 62 years of age, with visual acuity 6/24 6/9, 6/6 6/9, and 6/5 6/9 respectively in the right and left eyes. They were asymptomatic. Disc drusen were bilateral and showed a typical signet-like extension towards the macula on fluorescein angiography. There was a marked contrast between the degree of preserved good vision and extensive pigment dystrophy affecting the papillomacular bundle area. Case 7 of the St Louis series[2] and case 6 of the New York series[5] showed similar fundus changes. A similar contrast was seen in most cases of groups II and III, where the function of the macula seems to have recovered in time in spite of marked pigment thinning or clumping (Figs. 8 and 9).

Discussion

The purpose of putting on record this clinical material is to add a considerable number of cases to those hitherto reported. The opportunity to follow them for a period of up to 10 years (average 5 years) helped to establish the natural history and the character of the syndrome. We propose to call it the Optic Disc Drusen Retinopathy. The manifestations of the syndrome areas follows.

DRUSEN

Drusen of the optic disc which may be 'buried' and clinically manifest only as a filling of physiological cupping and an impression of a small pink dark circled optic disc, but where fluorescein angiography reveals their presence. The drusen may affect the marginal area of the disc, clinically deforming it. The drusen may also seem to be separated from the edge of the disc, although usually close to it, but fluorescein angiography in these cases demonstrates a plateau of staining, involving both the drusen and the disc.

HAEMORRHAGES

Haemorrhages start always at the edge of the disc or an extending drusen. They may be limited to the disc surface (splinter haemorrhages) or its rim and immediate vicinity (group I of our series). When located at the rim they seem dark red and used to be described as 'deep' haemorrhages. They can be proved by the use of red-free photography to be quite superficial (intra-retinal) and some were demonstrated to be placed in the nerve fibre layer, in front of the retinal blood vessels. The darker colour and slowness of absorption of some 'deep' haemorrhages may signify their location posterior to the neuroepithelial layers of the retina, but still in front of pigment epithelium. A fine meshwork of disc surface vessels may accompany them. They may be recurrent, but they do not permanently interfere with visual acuity. They may rupture through the internal limiting membrane into the vitreous.

A second type of haemorrhage while starting at the edge of the disc extends from there temporally in bright red sheets and splashes. The haemorrhage may originate at a drusen body located at the nasal edge of the disc and then it extended into the nasal retina. The resolution is identical with the temporally located haemorrhages, but the macula is clearly not involved. In all other cases the haemorrhage even if not quite reaching the macula is preceded by an area of fluid dissecting the retina.

These haemorrhages can be proved to be intraretinal by slit lamp observation or red-free photography. A change in the character of the haemorrhage from this type to the 'deep' disc edge type was observed on recurrence. The absorption of this 'deep' haemorrhage takes many months, while the peripheral haemorrhages absorb within a 2–4 months period.

SEROUS EXTRAVASATION

The haemorrhages dissecting the retina from the direction of the disc towards the macula as a rule do not reach the macula itself. Their advancing edge is, however, preceded by serous effusion which does. Optic disc drusen maculopathy may present without haemorrhages, but with serous extravasation only. It causes similar visual symptoms and it takes a similar amount of time to regress. The signs of retinal schisis may be very clear in these cases and the fluorescein angiography shows the usual disc drusen pattern. The change from the serous type of retinopathy to the classical haemorrhagic type was observed in a recurrence.

We propose that the vascular extravation could either be severe causing bleeding, but in less compromised circumstances only the serum may leave the blood vessels.

RETINAL MOUNDS

The degree of macular oedema and the oedema of the drusen themselves may be severe in some cases, throwing the retina into striate folds and tenting it from the drusen across the macula towards the periphery. The drusen in these cases are very elevated and situated over the disc edge or even seemingly outside its outline. As the resolution progresses these drusen, often covered initially by haemorrhages, settle, shrink, and eventually lose their slaty colour. They either become whitish ovoid nodules spattered by black pigment spots or form solid greyish-yellow scars. In spite of being usually placed in the papillo-macular bundle area at the temporal side of the disc they cause no nerve bundle scotoma. It must have been the early clinical stage of such a case which led to the erroneous diagnosis of a melanoma in Sanders *et al.*'s report[1] on case 3.

'HISTOPLASMA' SPOTS

Although not a regular feature of the syndrome they are worth noting. In 2 patients the equatorial areas of both fundi showed a scatter of small, round, yellowish spots, some with central pigment clumps. In one of them a slaty, irregular tract of pigmented scar was seen in the temporal periphery. In another case small choroidal scars developed during the follow-up. The process was observed as starting with focal retinal oedema without signs of inflammation. Similar 'histoplasma' spots were described by Wise *et al.*[3] in their case 7. It is tempting to consider the whole optic disc drusen retinopathy syndrome as a manifestation of parasitic infestation, but in neither of these cases, or indeed in any reported cases, were the results of specific tests abnormal. The significance of 4 such affected cases among those on record is unclear.

DIFFERENTIAL DIAGNOSIS

The cases of optic disc drusen retinopathy confined to bleeding at the optic disc only (group I) require differentiation from papilloedema; with the use of fluorescein angiography this has ceased to be a major problem.

The cases presenting an acute picture with retinal haemorrhages require differentiation from disciform senile degeneration, parasitic infestation, and melanoma. The differentiation from disciform degeneration is important in respect of prognosis. Optic disc drusen retinopathy is likely to resolve within a few months with restoration of vision (Fig. 10), while Bruch's membrane degeneration leads to serious loss of sight. It is the demonstration of drusen and the absence of subretinal vessels which are crucial. The age of the patient is a much less valuable help in diagnosis. Patients over 60 are among those affected by optic disc drusen retinopathy, while patients of any age may develop disciform response foci.

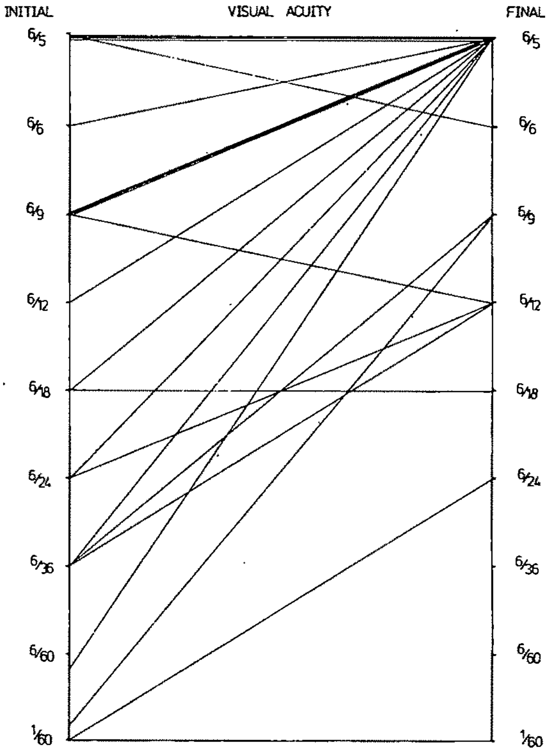

Fig. 10 *Visual acuity changes, groups I, II, and III (including 4 recurrences).*

Parasitic infestation should be accepted only if appropriate laboratory tests prove positive. To mistake a pigmented posthaemorrhagic mound for a malignant tumour would nowadays be unlikely.

The bloodless forms of the syndrome should be kept in mind in cases of spontaneous macular retinoschisis, and here the use of fluorescein angiography with its typical signet-like staining of drusen, which may not be obvious clinically, is helpful. Even the development of pigmentary macular changes is compatible in this type of maculopathy with preservation of good vision. The burnt-out, late picture of optic disc drusen retinopathy may help in the diagnosis of some macular degenerations, especially if unilateral, irrespective of age. Finally, the very crucial characteristic of the optic disc drusen retinopathy is the fact that it is a self-limiting disease with a good visual prognosis.

HISTOPATHOLOGY

Sanders *et al.*[2] reported histological findings of a 12-year-old boy's eye which was enucleated on the suspicion of a malignant-melanoma-like nodule situated near the temporal edge of the optic disc (case 3). The histological section showed a haematoma located between the neuroepithelial retina and pigment epithelium which seemed intact. The section also showed large drusen of the affected disc.

Our clinical observations clearly fit the histologically demonstrated localisation of the haemorrhage in front of the epithelium. They place the haemorrhages and serous extravasation certainly in front of the pigment epithelium and probably wholly intraretinally—between the internal and external limiting membranes. In some cases pigment epithelium showed in later stages patchy depigmentation, but there was never any evidence of blood vessels invading under the retina through Bruch's membrane. This fundamental difference between optic disc drusen retinopathy and those connected with Bruch's membrane insufficiency could explain the very different prognosis and self-limiting, benign course of optic disc drusen retinopathy.

On pathogenesis and aetiology of optic disc drusen retinopathy we can only offer speculation. Drusen of the optic nerve are always located in front of the lamina cribrosa. The area is supplied by small vessels from the ciliary circulation, and it is from these vessels that the extravasation must come. Whether it is because of mechanical injury to the vessels by sharp edges of the calcified drusen, or their pressure on the venous outflow, whether the congestion and subsequent bleeding are caused by choking of the optic disc by orthograde axoplasmic neuronal flow and mitochondrial debris we do not know.[8]

The second unknown is related to the way in which the blood specifically finds its way to dissect the retina or its interface with pigment epithelium. The movements of blood would then have to be through the junctional tissue of Kuhnt, where the retinal layers end at the margin of the optic nerve. In this respect there seem to be some similarities between disc drusen retinopathy and retinopathy connected with optic disc pits.[9]

An increased awareness of the syndrome would certainly make a larger number of cases available for study. An extended follow-up time, combined with a donor eye index, should in time yield necropsy material for electron microscopy of the crucial junctional area between the retina and the optic disc.

Our thanks are due to our colleagues in and outside the Birmingham and Midland Eye Hospital for referring the patients, and particularly to Mr Vernon Smith, who contributed several cases; to Mrs Ryan and Mrs McKoy for their clerical and nursing help at the Angiography-Laser Department; to a succession of our junior staff whose enthusiastic interest in these patients made us put our observations on record; and to Sandra Starkey for her patience and competence in preparing the manuscript.

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British Journal of Ophthalmology, 1982, **66**, 96–98

Optic nerve glioma and neovascular glaucoma: report of a case

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SUMMARY Neovascular glaucoma in a blind eye was a complication of an enlarging intraconal optic glioma in an 11-year-old girl. Venous stasis retinopathy was observed several months before the appearance of iris neovascularisation and elevated intraocular pressure. We suggest that venous stasis retinopathy in a patient with optic glioma is a reasonable indication for resection of the intraconal portion of the tumour.

Neovascular glaucoma is an unusual complication of optic nerve glioma. This report describes a young patient with monocular blindness from an enlarging intraconal optic glioma. After a progressive increase in proptosis she developed venous stasis retinopathy and neovascular glaucoma.

Case report

The patient, an 11-year-old girl, was first seen by her ophthalmologist in December 1978 after a school nurse discovered that she had defective vision in her left eye. Visual acuity in this eye improved from 6/7·5+4 to 6/6+4 with a −0·75 dioptre spherical lens. Vision in her right eye was 6/6+4 unaided, but she had a 1+ afferent pupillary defect and mild swelling of the optic disc in this eye. The left disc was normal. Colour vision, extraocular movements, and exophthalmometer readings were normal. Examination with a slit-lamp showed no abnormalities. The intraocular pressure was 15 mmHg bilaterally. A visual field examination revealed a relative defect in the inferior nasal quadrant of the right eye. The left visual field was full.

A computerised tomography (CT) scan showed fusiform, intraconal enlargement of the right optic nerve to 2-3 times its normal diameter, the enlarged segment extending from immediately behind the globe to the orbital apex. The right optic canal was enlarged. There was no evidence of intracranial extension. The intracranial optic nerve, suprasellar cistern, and ventricles were normal. Tomograms showed enlargement of the right optic canal at both its orbital and intracranial ends; its orbital diameter was 1·5-2·0 mm greater than that of the left canal. The walls of the canal were normal. Pneumoencephalography with polytomography confirmed that the intracranial segment of the right optic nerve was normal in diameter. A glioma was suspected. A general physical examination revealed no signs of neurofibromatosis.

Three months later the patient complained of painless dimming of vision in the right eye. Visual acuity was 6/9 unaided, improving to 6/7·5 with correction; 1·5 mm of proptosis and a 4+ afferent pupillary defect were noted. Swelling and congestion of the right optic disc were noticeably greater than before. Visual field loss was more marked, with an inferior altitudinal defect to small targets.

In November 1980 visual acuity in the right eye had deteriorated to the extent that she could see to count fingers at 6 inches (15 cm) in one quadrant only. Right proptosis had increased to 3 mm. Intraocular pressure was 17 mmHg bilaterally. Swelling of the right disc had increased, and there was marked venous stasis retinopathy, with optociliary shunt vessels and intraretinal haemorrhages around the optic nerve head. The left disc was normal (Fig. 1).

A month later she had 2 episodes of acute pain in her right eye, each of which resolved spontaneously. She was admitted to hospital for further examination. She was unable to perceive light and had 12 mm of axial, irreducible proptosis in her right eye. The eye showed marked ciliary injection. The right pupil was fixed in response to light stimulation and was widely dilated

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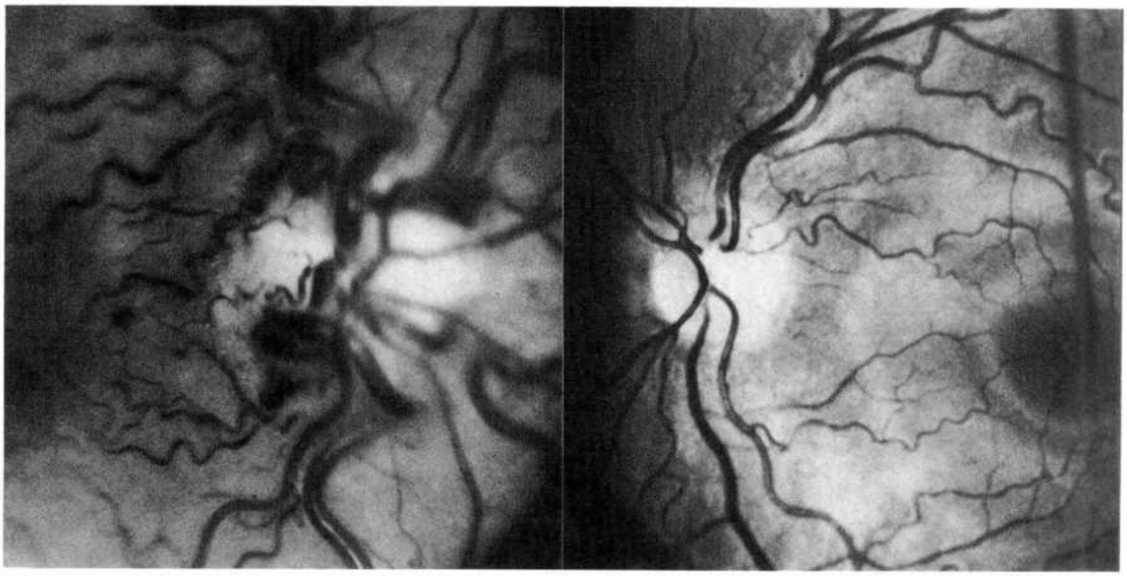

Fig. 1 *Fundus photographs of both eyes. The right disc is swollen and shows marked venous stasis retinopathy, optociliary shunt vessels, and intraretinal haemorrhages around the optic nerve head. The left disc is normal.*

(10 mm). Examination with a slit-lamp revealed corneal oedema, a shallow anterior chamber, and extensive neovascularisation and atrophy of the iris (Fig. 2). The angle of the anterior chamber was completely closed by neovascular membrane over 360 degrees. Intraocular pressure 49 mmHg. The right disc was pale and swollen and showed signs of marked arteriolar narrowing, marked venous dilatation, scattered venous haemorrhages, and optic disc atrophy. A second CT scan showed enlargement of the intraconal optic nerve mass and contrast enhancement of the periphery of the tumour (Fig. 3). The suprasellar cistern and intracranial optic nerves were normal.

Through a Kronlein orbitotomy the anterior portion of the tumour was excised from directly behind the globe and as far posteriorly as the exposure would allow. Histopathological examination showed a pilocytic astrocytoma; the central retinal vein was not occluded, and the central retinal artery was not identified. Postoperatively the intraocular pressure was 42 mmHg. The retinal arterioles were bloodless and barely visible; the retinal veins contained blood but were small. The patient's eye remains pain-free with topical medical therapy.

Discussion

Neovascular glaucoma is a rare complication of an optic nerve glioma. It has been reported in 2 cases of small gliomas, following central retinal vein occlusion in one case[1] and following anterior segment ischaemia in the other.[2] The initial manifestation of an optic glioma in our patient was visual loss and swelling of the optic disc. Progressive enlargement of the tumour, observed clinically and by CT, was associated with (1) increasing proptosis, (2) decreased vision, (3) progressive optic atrophy and optociliary

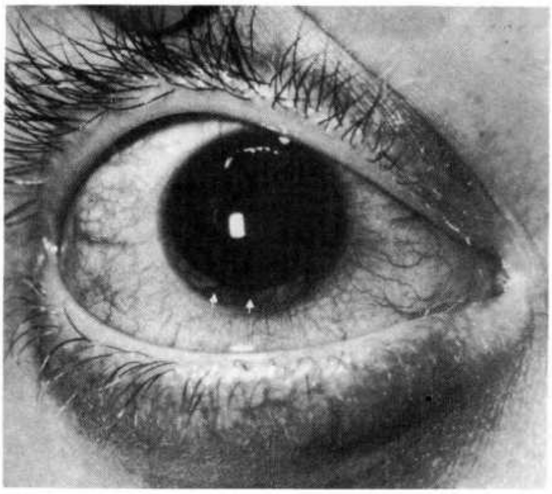

Fig. 2 *Right eye showing marked ciliary injection and extensive atrophy and neovascularisation of the iris (arrows).*

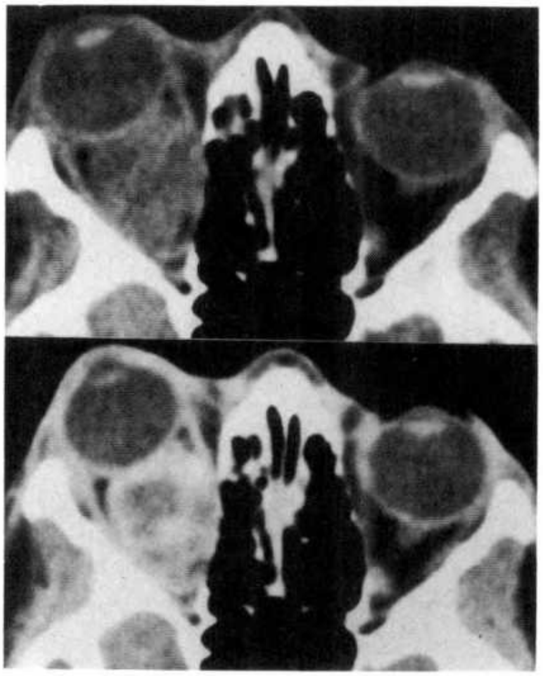

Fig. 3 *Precontrast (above) and postcontrast (below) axial computerised tomography scans, the latter showing peripheral enhancement of the large optic nerve glioma.*

shunts, (4) signs of venous stasis retinopathy, and (5) neovascularisation and extensive atrophy of the iris with subsequent neovascular glaucoma.

The pathogenesis of rubeosis iridis and neovascular glaucoma is not fully understood. Ashton[3] proposed that ischaemic retina releases a vasoproliferative factor that diffuses into the aqueous humour, producing neovascularisation of the iris and the angle of the anterior chamber, and glaucoma.

Iris neovascularisation and neovascular glaucoma have been observed (1) following ischaemic central retinal vein occlusion,[4 5] (2) secondary to occlusion of the central retinal artery, either alone[6 7] or in combination with occlusion of the ciliary arteries by emboli or in temporal arteritis,[8 9] and (3) as a complication of chronic retinal detachment.[10 11]

We believe that iris neovascularisation and neovascular glaucoma in our patient were the result of the adverse effects of the enlarging tumour on the ciliary and retinal circulation and subsequent retinal ischaemia. Venous stasis retinopathy, marked retinal arteriolar narrowing, and extensive atrophy of the iris, together with a markedly dilated pupil, provided further evidence of retinal and ciliary ischaemia.

Preservation of the eye is a major objective in the management of orbital optic glioma.[12] Our case illustrates how this goal was compromised by the development of neovascular glaucoma while the patient awaited a cosmetic operation to relieve proptosis. Although this complication is very rare, we now believe that venous stasis retinopathy in a patient with an optic glioma is a reasonable indication for resection of the intraconal portion of the tumour.

This study was supported in part by fellowship grants from the Royal College of Surgeons of England, Keeler Instruments, Ltd (UK), and the Eastern Health and Social Services Board, Northern Ireland. The authors thank Susan Eastwood for editorial assistance and Beverly J. Hunter for preparation of the manuscript.

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British Journal of Ophthalmology, 1982, **66**, 99–101

Disc assessment and visual field analysis in a hospital glaucoma population

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SUMMARY A hospital series of 432 patients with glaucoma was studied to quantify the ease of assessment of the cup/disc ratio and the visual fields. 19·9% of the discs were not easily visible to monitor accurately ophthalmoscopically and a further 27·9% were grossly cupped. 63% of the patients studied had general features or ocular pathology which might contribute to unreliable analysis of the visual field.

The 3 prime variables monitored during the management of glaucoma are the level of intraocular pressure, the appearance of the optic nerve head, and the state of the visual fields. It is usually the level of the intraocular pressure relative to the other 2 variables which determines the cardinal management decisions of either the initiation of life-long medical treatment or potentially sight-threatening drainage surgery.

In 'low-tension glaucoma' the visual field may deteriorate with intraocular pressures of less than 20 mmHg. An attempt to reduce this by drainage surgery may result in macular oedema and a dramatic fall in visual acuity. Thus a deteriorating visual field alone might not persuade all clinicians to risk macular function by surgery when the intraocular pressure is in the low-normal range. Hence the only absolute criterion for treatment or surgery in an eye with useful function is a very high intraocular pressure. In its absence decisions on management are a matter of individual clinical judgment, taking account of relative changes in these 3 main factors. Other features which influence the clinician include a family history of glaucoma, the age and general health of a patient and his life expectancy, pathological myopia, a central venous occlusion in the fellow eye, the total visual reserves, and the differences between the presenting and current intraocular pressures.

A decision on management is therefore based on the relative changes in the 3 prime variables with numerous background factors. The availability of accurate prime data when making the 2 cardinal management decisions can be of crucial importance.

This paper attempts to quantify within a short time scale in the life history of a hospital glaucoma population 2 of these variables, namely, the availability and reliability of the optic disc appearance and the accuracy of visual field analysis.

Materials and methods

The ocular and general clinical status of 432 patients who are currently under observation for glaucoma was analysed from their hospital records. The data referring to the discs related to their clinic attendances in 1978. They were unselected and formed the bulk of the hospital glaucoma population.

There were 792 affected eyes (56 fellow eyes had normal discs and intraocular pressures, and 16 eyes had been enucleated). 496 eyes had chronic simple glaucoma, 77 had subacute angle closure. The remaining 219 were a mixed group consisting largely of patients with chronic closed-angle glaucoma, ocular hypertension (pressure >30 mmHg), post-uveitic glaucoma, and aphakic and post-traumatic glaucoma. The number of optic discs that could be assessed accurately with the ophthalmoscope (after attempted pupillary dilatation where necessary) was recorded. The number of eyes in which changes in the optic disc could contribute to management was quantified. Associated ocular and general clinical features adversely influencing the accuracy of visual field analysis were assessed. These patients had been tested with the Bjerrum screen or the Friedmann visual field analyser for central field defects. Peripheral fields were tested with the Aimark perimeter in most cases, and a small group was tested with the Goldmann perimeter. A substantial minority with gross field loss to confrontation had not been further tested. No attempt was made to relate any inaccuracy of analysis to the method of field testing. The inves-

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tigative effort was confined to the identification of associated ocular or general features militating against the reliability of future changes.

Results

OPTIC NERVE HEAD APPEARANCE

Availability of accurate data. In 158 of the 792 eyes with glaucoma examined it was not possible ophthalmoscopically to measure the cup/disc ratio accurately. The factors responsible for this were cataract (118 eyes), corneal opacity (5 eyes), central venous thrombosis (4 eyes). Extreme miosis with synechiae, high myopia, and congenitally abnormal discs prevented valid assessment in 31 eyes.

Relevance for future management. 221 eyes had grossly cupped discs with cup disc ratios of 0·8 or greater (maximum diameter of cup was taken irrespective of meridian). These discs were so cupped that their potential for further change was profoundly reduced.

Of the remaining 413 eyes 63 had gross field loss consisting of 2 or more quadrants lost to confrontation. In these eyes visual reserves were extremely low, and one would not normally wait for further deterioration in fields or disc appearance. Management was therefore based almost entirely on the level of intraocular pressure. A further 109 eyes had control of pressures at 18 mmHg or less.

VISUAL FIELDS

This study was limited to the 573 eyes with chronic simple and subacute angle closure glaucoma. 361 eyes of the 573 examined had general and/or ocular features which made field analysis potentially unreliable.

(A) Associated ocular features adversely influencing the accuracy of visual field analysis. In 292 of these 573 eyes examined it was not possible to rely on field tests for evidence of progression of visual field loss to make decisions in management because of associated ocular pathology. The dominant factors responsible were: (1) lenticular: cataract and aphakia (215 eyes); the visual acuity was less than 6/12 in the phakic eyes in this group, and a small minority were aphakic at the time of analysis; (2) maculopathy (65 eyes); (3) retinal vein occlusion (28 eyes); (4) other pathology (keratopathy, retinal detachment, pathological myopia, 5 eyes). Some of the eyes in 1–4 had more than the one condition.

(B) Associated general features adversely influencing the accuracy of visual field analysis. In 162 eyes of the 573 examined there were general features present which were a potential source of error in the use of field tests for evidence of progression of visual field loss. The chief factors responsible for this were: (1) senility (65 patients, 130 eyes); (2) extreme deafness (10 patients, 20 eyes); (3) mental subnormality or illness (6 patients, 12 eyes).

Groups (A) and (B) were not mutually exclusive.

Discussion

The ideal patient with glaucoma is a reliable witness, with good concentration, is emmetropic with clear media, and has a healthy fundus and an easily described disc. In clinical practice such patients are a minority. This may not be so evident in a group of glaucoma patients studied only at presentation. The effects of increasing age and duration of glaucoma and its treatment result in a changing associated morbidity precluding the ideal situation. A hospital glaucoma population consists largely of such patients, and this study attempts to emphasise the limitations of their assessment.

Estimation of a reliable intraocular pressure was not found to present a significant problem. The occasional patient with bullous keratopathy or corneal scarring necessitated a Schiøtz measurement rather than applanation tonometry. This was not so, however, with the other objectively obtained prime variable—the configuration of the optic nerve head. In 158 eyes (19·9%) of the 792 glaucomatous eyes examined it was not possible to measure the cup/disc ratio. Ophthalmoscopically most of the 11 parameters of the optic disc given importance by Drance[1] and the detailed changes of Hitchings and Spaeth[2] would have been unavailable in a higher percentage of eyes. Likewise photography, stereophotography, stereogrammetry, and coloriometry would have been inapplicable to this group. Mydriatic examination with a fundus contact lens might have helped in assessing some of the discs in cataractous eyes in the earlier stages.

221 (27·9%) further eyes had grossly cupped discs with cup disc ratios of 0·8 or greater on direct ophthalmoscopy. As these discs were so cupped, it would be difficult to monitor the course of the glaucoma on the disc appearance, though serial photography if practical might have provided further information in selected cases. More reliance had to be placed either on field changes or on the level of intraocular pressure. It could be argued that discs with cups which extend to the edge on one side with a rim of one-fifth of a disc diameter on the other side could be monitored, but the wisdom of operating on such marginal disc changes alone is debatable.

Of the remaining 413 eyes 63 had extensive visual field loss (2 or more quadrants absent to confrontation). Disc appearances in these patients did not contribute to their management, as any residual ocular hypertension in isolation induced a decision for drainage surgery in eyes with advanced disease. It is not possible to define a precise level of 'residual hypertension'. This level would vary with the pressure found at initial presentation, possible contralateral venous thrombosis, and other background clinical features in eyes with such advanced disease.

Thus in 442 (55·8%) of the 792 eyes details of the optic nerve head were unavailable or of doubtful contribution in management.

Of the remaining 350 eyes there were 109 in which the intraocular pressures were under 18 mmHg. At this level of intraocular pressure it would be expected that very few eyes would show increase in disc cupping. In those few eyes that did develop progressive disc cupping the possible advantages gained by reducing the pressure further would have to be balanced against the complications of intraocular surgery, namely, cataract formation and possible macular or disc oedema due to hypotony. In such a situation many clinicians would consider a slow natural erosion of visual reserves preferable to a risk of abrupt deterioration from surgical complications. Although optic disc changes in this group might occasionally indicate the need for phasing, checking for overenthusiastic treatment of hypertension, anaemia, or viscosity syndromes, these patients were in reality monitored by their intraocular pressure in isolation. Their discs were of potential value in management only if pressure control was lost.

At the time of analysis therefore in 551 (69·5%) of the 792 eyes the optic disc appearance was not of great relevance in the management of the glaucoma.

The visual field changes are a subjective measurement and were also found to be potentially unreliable in a greater number of patients. In 292 (50·9%) of the 573 eyes with a chronic simple or subacute angle-closure glaucoma there were associated ocular features militating against the accuracy and hence reliability of field testing. The commonest cause was cataract. The number of cataracts invalidating serial field analysis was found to be greater than that precluding accurate disc appraisal. The coexistence of cataract with glaucoma influencing the accuracy of visual field has been discussed previously. Miller and Karseras[3] and Playfair and Watson[4] have noted an apparent worsening of visual field, which has subsequently improved after cataract extraction. The present analysis attempts to quantify this potential source of error. Cataract and other associated ocular morbidity will increase with duration of attendance at glaucoma clinics, and the relevance of serial refined visual field analysis in most patients with glaucoma can be seriously questioned. The more sophisticated the method of analysis, the more difficult it is to interpret the significance of the changes found in this group.

In addition to this potential source of error is the subjective nature of the response in a largely elderly population. Reliable perimetry was doubtful in 162 eyes of 573 reviewed because of the patient's general status. It was found that a total of 361 eyes of the 573 reviewed (63·0%) had general and/or ocular features potentially contributing to unreliable field analysis.

The clinician should thus be aware that the data complex forming the basis of his decisions changes during the course of the disease, and may be or become greatly deficient in accuracy and availability because of the increasing associated morbidity and age changes.

We thank Robert Newcombe, PhD, who did the computer analyses.

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British Journal of Ophthalmology, 1982, **66**, 102–108

Addition of pindolol to routine medical therapy: a clinical trial

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SUMMARY A double-blind study of pindolol eye drops 0·5% was carried out on 24 patients with primary open-angle glaucoma. Pressures were taken once weekly during three 3-week periods. In one of these periods placebo was given in both eyes, during another pindolol was given in one eye, and during another it was given in the other eye. A drop in pressure averaging 2·79% was found in eyes receiving pindolol compared with the period when they were receiving saline. Substantial placebo effects were found when in-trial pressures were compared with pretrial, but the placebo effects were avoided in the analysis of the pindolol effect. Blood pressure and pulse rates were not significantly affected. There was slight evidence of pindolol in one eye affecting the contralateral eye but little evidence of persistence of hypotensive effects after cessation of treatment.

The ocular hypotensive effect of pindolol has been described by various authors including Bonomi and Steindler[1] and S. E. Smith *et al.*[2]

The study about to be described was an appraisal of the pressure-lowering effect of topical pindolol while patients with chronic glaucoma continued to take their usual medication. Thus the protocol was similar to that employed by R. Smith *et al.*[3] in respect of timolol. The arrangements were, however, not identical in that a double placebo period was introduced which had not been employed in the prior study.

Patients and methods

Twenty-four patients with chronic primary open-angle glaucoma were selected. They were already taking local medication but not acetazolamide. The majority were on pilocarpine plus guanethidine and adrenaline. They were asked if they were willing to try a new drug in addition to their existing treatment and their consent was obtained before entering them into the trial. The selection was limited to patients of 40 years or more, male or female, with a pulse rate of 61 or more and a blood pressure of at least 120/70 mmHg.

At an initial session the following data were recorded: name, age, sex, intraocular pressure in each eye, date and time of measurement, visual acuity, blood pressure, and pulse rate. Existing therapy was continued and the Pharmacy issued 2 extra identical bottles, one containing normal saline and the other either normal saline or pindolol 0·5% (Moorfields formulation). Patients were instructed to instil one drop into the right eye from the bottle so marked and one into the left eye from the other bottle each morning and evening for one week, including the morning of the next visit. One week later the patients were reviewed and again on 2 more weekly visits. Then the therapy was altered for a further 3-week period and once more for a final 3-week period. All the examinations were carried out at about the same time of day in each patient.

The administration of pindolol or saline to one eye and saline to the other was arranged so that by the end of the trial each patient had had a 3-week period of drug in one eye and saline in the other, a period the other way round, and a period with saline in both eyes. It was arranged that one-third of the patients received double saline in the first, second, or last periods respectively. The trial was carried out double-blind, and the Pharmacy held the code, which was not broken until the trial was completed.

FORMULATION

Both pindolol and placebo drops were prepared in

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the Hospital Pharmacy and put up in identical packs. The only information given was the trial number of the patient, the treatment period, and the eye for which the bottle was to be used (right or left). The name and concentration of preservative was given (benzalkonium chloride was used in both active and placebo drops). Batch numbers were varied in each treatment period, though all drops were prepared at the same time, to prevent identification of the active drug by means of the batch number.

AIMS AND OBJECTS

The objects of the trial were first to confirm that pindolol has a pressure-lowering effect in chronic open-angle glaucoma; secondly to find what effect, if any, pindolol has on the pressure of the contralateral untreated eye; thirdly to determine the duration of effect of pindolol after administration has been stopped; fourthly to determine the effect of topical pindolol on the pulse rate and blood pressure; and finally to see if there are any obvious short-term side effects.

Results

BASELINE DATA

The mean age of the patients was 63·8 with a range of 41 to 81 and a standard deviation of 9·01. The mean pretrial blood pressure was 149/88 mmHg, and the mean pretrial pulse rate 77·66. There were 6 females and 18 males.

INTRAOCULAR PRESSURE

It might be supposed that the simplest way to study the effect of pindolol on the intraocular pressure would be to take the mean of the pretrial pressures and of the pressures during the use of pindolol and compare them; and indeed if this is done a clear-cut difference is found, pretrial pressures averaging 24·89 mmHg and pressures on pindolol averaging 18·37, a difference of 6·52 mmHg or about a 25% drop in pressure (Table 1).

Unfortunately there is also a substantial reduction of pressure with the placebo drops, pretrial pressures again 24·89 and pressures on placebo averaging 21·10, a difference of 3·79 or 15%. This placebo effect may have been due to the more conscientious use of other medication in the patients under study.

On the assumption that the patient's compliance improved throughout the trial it would probably be better for all further comparisons to be made between

Table 1 *Comparison of pressures (mmHg), all eyes*

Pretrial pressures		*Pressures on pindolol*
n = 48·00 (observations)		n = 144·00 (observations)
ϵ = 1195·00		ϵ = 2696·00
m = 24·89	[D = 6·52]	m = 18·37
s = 6·29		s = 4·41
var = 38·80		var = 19·39
Pretrial pressures		*Pressures on double saline*
n = 48·00 (observations)		n = 144·00 (observations)
ϵ = 1195·00		ϵ = 3039·00
m = 24·89	[D = 3·79]	m = 21·10
s = 6·29		s = 6·02
var = 38·80		var = 36·10

Table 2 *Comparison between pressures of the 8 eyes which had double saline in the first period (SS1S) and the same eyes when on pindolol (SS1P)*

Patient	*SS1S*		*SS1P*		*Differences*			
					Right eyes		*Left eyes*	
	R	*L*	*R*	*L*	*S-P*	*(S-P)^2*	*S-P*	*(S-P)^2*
3	26	26	19	18	7	49	8	64
	24	21	15	20	9	81	1	1
	27	24	20	21	7	49	3	9
6	38	28	27	26	11	121	2	4
	33	29	26	23	7	49	6	36
	35	28	26	25	9	81	3	9
8	22	22	20	17	2	4	5	25
	24	24	18	18	6	36	6	36
	22	22	18	18	4	16	4	16
11	14	16	11	14	3	9	2	4
	14	18	11	14	3	9	4	16
	16	17	13	14	3	9	3	9
13	16	19	18	25	−2	4	−6	36
	16	23	18	22	−2	4	1	1
	17	20	17	21	0	0	−1	1
16	26	22	18	17	8	64	5	25
	22	21	17	20	5	25	1	1
	22	23	17	21	5	25	2	2
19	19	15	16	14	3	9	1	1
	16	14	12	14	4	16	0	0
	16	14	15	14	1	1	0	0
24	26	36	26	27	0	0	9	81
	30	42	25	25	5	25	17	289
	28	38	26	29	2	4	9	81

R Saline		*Pindolol*	*L Saline*		*Pindolol*
n = 24·00		24·00	24·00		24·00
ϵ = 549·00		449·00	562·00		477·00
m = 22·87	[D = 4·17]	18·70	23·41	[D = 3·54]	19·87
sD = 6·76		4·96	7·28		4·67
var = 43·77		23·62	50·82		20·94

Comparing means as paired data	*Comparing means as paired data*
ϵRS-RP = 100·00	ϵLS-LP = 85·00
ϵ(RS-RP)^2 = 690·00	ϵ(LS-LP)^2 = 747·00
MD = 4·17	MD = 3·54
S diff = 3·37	S diff = 4·31
SEM diff = 0·70	SEM diff = 0·90
t = 5·95	t = 3·93
p < 0·001	p < 0·001

Table 3 *Comparison between pressures of the 8 eyes which had double saline in the second period (SS2S) and the same eyes when on pindolol (SS2P)*

Patient	*SS2S*		*SS2P*		*Differences*			
					Right eyes		*Left eyes*	
	R	*L*	*R*	*L*	*S-P*	*(S-P)^2*	*S-P*	*(S-P)^2*
2	26	14	26	13	0	0	1	1
	24	13	26	13	−2	4	0	0
	30	10	27	13	3	9	−3	9
4	19	18	16	15	3	9	3	9
	18	17	19	16	−1	1	1	1
	18	17	17	18	1	1	−1	1
9	18	16	20	15	−2	4	1	1
	19	18	21	16	−2	4	2	4
	25	22	19	20	4	16	2	4
12	16	17	16	18	0	0	−1	1
	22	24	16	13	6	36	11	121
	18	18	18	15	0	0	3	9
14	31	32	28	28	3	9	4	16
	32	28	28	29	4	16	−1	1
	40	32	25	27	5	25	5	25
18	22	20	16	16	6	36	4	16
	23	19	16	16	7	49	3	9
	25	26	20	18	5	25	8	64
20	24	18	20	18	4	16	0	0
	25	19	20	20	5	25	−1	1
	24	20	22	17	2	4	3	9
22	12	24	12	16	0	0	8	64
	12	20	10	16	2	4	4	16
	12	21	10	17	2	4	4	16

	R Saline		*Pindolol*	*L Saline*		*Pindolol*
n =	24·00		24·00	24·00		24·00
ε =	533·00		468·00	483·00		423·00
m =	22·20	[D = 2·70]	19·50	20·13	[D = 2·51]	17·62
sD =	6·70		5·24	5·40		4·47
var =	43·08		26·33	27·94		19·15

Comparing means as paired data

εRS-RP = 55·00
ε(RS-RP)^2 = 297·00
MD = 2·70
S diff = 2·67
SEM diff = 0·56
t = 4·82
p < 0·001

Comparing means as paired data

εLS-LP = 60·00
ε(LS-LP)^2 = 398·00
MD = 2·51
S diff = 3·21
SEM diff = 0·67
t = 3·74
p < 0·01

Table 4 *Comparison between pressures of the 8 eyes which had double saline in the third period (SS3S) and the same eyes when on pindolol (SS3P)*

Patient	*SS3S*		*SS3P*		*Differences*			
					Right eyes		*Left eyes*	
	R	*L*	*R*	*L*	*S-P*	*(S-P)^2*	*S-P*	*(S-P)^2*
1	17	16	17	18	0	0	−2	4
	18	16	15	18	3	9	−2	4
	18	15	15	17	3	9	−2	4
5	21	20	22	24	−1	1	−4	4
	21	19	20	18	1	1	1	1
	21	20	20	19	1	1	1	1
7	19	13	18	12	1	1	1	1
	20	16	18	12	2	4	4	16
	20	15	20	12	0	0	3	9
10	20	17	17	14	3	9	3	9
	24	20	22	18	2	4	2	4
	26	20	18	18	8	64	2	4
15	15	16	14	13	1	1	3	9
	14	16	14	14	0	0	2	4
	16	18	18	14	−2	4	4	16
17	26	20	21	15	5	25	5	25
	23	22	20	16	3	9	6	36
	25	22	20	20	5	25	2	4
21	15	26	18	24	−3	9	2	4
	16	26	14	24	2	4	2	4
	17	32	15	20	2	4	12	144
23	16	18	12	14	4	16	4	16
	14	14	11	17	3	9	−3	9
	16	17	16	15	0	0	2	4

	R Saline		*Pindolol*	*L Saline*		*Pindolol*
n =	24·00		24·00	24·00		24·00
ε =	458·00		415·00	454·00		406·00
m =	19·08	[D = 1·79]	17·29	18·92	[D = 2·01]	16·91
sD =	3·71		3·05	4·36		3·67
var =	13·24		8·95	19·24		12·90

Comparing means as paired data

εRS-RP = 43·00
ε(RS-RP)^2 = 209·00
MD = 1·79
S diff = 2·34
SEM diff = 0·49
t = 3·65
p < 0·01

Comparing means as paired data

εLS-LP = 48·00
ε(LS-LP)^2 = 336·00
MD = 2·01
S diff = 3·16
SEM diff = 0·66
t = 3·04
p < 0·01

pressures 'on saline' (or 'on placebo') and pressures 'on pindolol,' pretrial pressures being totally eliminated from the statistics. But the problem with this approach is that cross-over and/or follow-on effects may be operating.

In order to eliminate cross-over or follow-on effects the 8 patients (16 eyes) who took saline in both eyes for the first 3-week period (the SS1 patients) may be studied separately. Table 2 shows the findings. In these patients the mean pressures during the 3 weeks of placebo were 22·87 mmHg for right eyes and 23·41 for left eyes. The mean pressures in these same eyes during their later 3-week pindolol periods were 18·7 and 19·87 respectively, a difference of 4·17 for right eyes and 3·54 for left, differences which appear to be statistically significant.

Ignoring any possible follow-on effects for the moment but avoiding cross-over effects we can also study the 'double saline second' and 'double saline third' groups. As in the 'double saline first' (or SS1) group there are 8 patients and 16 eyes in each group.

In the SS2 patients (Table 3) the mean pressures on

Table 5 *Pressures on saline versus pressures on pindolol (all patients)*

Double saline				*Pindolol*
ε	=	3039·00		2638·00
m	=	21·10	[D = 2·79]	18·31
n (obs)	=	144·00		144·00
n (eyes)	=	48·00		48·00
SD	=	6·02		4·48
SD²	=	36·24		20·07
var	=	36·10		19·99

placebo were 22·2 mmHg for right eyes and 20·13 for left, and the mean pressures on pindolol were 19·5 for right and 17·62 for left, a difference of 2·7 for right and 2·51 for left. In the SS3 patients (Table 4) the mean pressures on placebo were 19·08 mmHg for right eyes and 18·92 for left and the pressures on pindolol 17·29 and 16·91, differences of 1·79 and 2·01 for right and left eyes respectively. All these differences are significant at least at the 0·01 level of confidence. Pooling the figures we can say that the difference between all eyes on double saline and all eyes on pindolol is 2·79 mmHg (Table 5).

(It should be emphasised that the comparison between saline and pindolol in all the above examples refers to the comparison between the 'double saline' pressures and the pindolol pressures. Pressures 'on saline' obtained while the other eye was on pindolol have not been used to avoid possible cross-over effects.)

Table 6 *Dosage schedule*

Patient	*Period 1*		*Period 2*		*Period 3*	
	R	*L*	*R*	*L*	*R*	*L*
3	S	S	P	S	S	P
6	S	S	S	P	P	S
8	S	S	P	S	S	P
11	S	S	P	S	S	P
13	S	S	S	P	P	S
16	S	S	S	P	P	S
19	S	S	P	S	S	P
24	S	S	S	P	P	S
2	S	P	S	S	P	S
4	P	S	S	S	S	P
9	S	P	S	S	P	S
12	S	P	S	S	P	S
14	P	S	S	S	S	P
18	S	P	S	S	P	S
20	P	S	S	S	S	P
22	P	S	S	S	S	P
1	P	S	S	P	S	S
5	S	P	P	S	S	S
7	P	S	S	P	S	S
10	P	S	S	P	S	S
15	S	P	P	S	S	S
17	P	S	S	P	S	S
21	S	P	P	S	S	S
23	S	P	P	S	S	S

Table 7 *SS2S eyes with prior pindolol versus without*

	SS2 with prior pindolol		*SS2 without prior pindolol*	
	R	*L*	*R*	*L*
2	—	14	26	—
	—	13	24	—
	—	10	30	—
4	19	—	—	18
	18	—	—	17
	18	—	—	17
9	—	16	18	—
	—	18	19	—
	—	22	23	—
12	—	17	16	—
	—	24	22	—
	—	18	18	—
14	31	—	—	32
	32	—	—	28
	40	—	—	32
18	—	30	22	—
	—	19	23	—
	—	26	25	—
20	24	—	—	18
	25	—	—	19
	24	—	—	20
22	12	—	—	24
	12	—	—	20
	12	—	—	21
n =	24·00		24·00	
ε =	484·00		532·00	
m =	20·16	[D = −2·0]	22·16	
SD =	7·21		4·71	
var =	49·88		21·30	

POSSIBLE 'FOLLOW-ON' EFFECT

The term 'follow-on' effect refers to the possibility of the effects of pindolol persisting for some time after administration had ceased.

The mean pressures during the double placebo periods seem to get lower the later the period occurs in the trial. If we study the administration code (Table 6) it is apparent that in the SS2 group 8 of the 16 eyes concerned had received pindolol at some prior period. In order to test whether prior pindolol had affected the SS pressures it was found possible in the SS2 group to compare the pressures *during the saline period* of those eyes which had not and those eyes which had received prior pindolol—a comparison which could not be made either in the SS1 or the SS3 group.

Table 7 illustrates this analysis. SS2S eyes which had had prior pindolol showed a mean pressure of 20·16 mmHg, whereas eyes with no prior pindolol showed a mean pressure of 22·16—a difference of −2·0 mmHg. Each refers to 24 observations in only 8 eyes, and the difference might simply be due to

Table 8 *SS2S eyes with and without prior pindolol*

	SS2S eyes 'with prior pindolol' while on pindolol		*SS2S eyes 'without prior pindolol' while on pindolol*	
	R	*L*	*R*	*L*
2	—	13	26	—
	—	13	26	—
	—	13	27	—
4	16	—	—	15
	19	—	—	16
	17	—	—	18
9	—	15	20	—
	—	16	21	—
	—	20	19	—
12	—	18	16	—
	—	13	16	—
	—	15	18	—
14	18	—	—	28
	28	—	—	29
	28	—	—	27
18	—	16	16	—
	—	16	16,	—
	—	18	20	—
20	20	—	—	18
	20	—	—	20
	22	—	—	17
22	12	—	—	16
	10	—	—	16
	10	—	—	17
n =	24·00		24·00	
ϵ =	406·00		418·00	
m =	16·91	[D = −3·0]	19·91	
SD =	4·66		4·58	
var =	20·82		20·15	

chance or to the fact that the 2 groups of 8 eyes were not comparable. The group with the higher pressures might tend to show higher pressures at other stages in the investigation. But this can be tested. It is possible next to compare these same eyes while on pindolol, when each should be at minimum pressure. If the same difference is found, it would be reasonable to assume that there was a constitutional difference and that there was therefore no likelihood of the −2·0 difference shown in Table 7 being of any particular significance. Table 8 supports this view, namely, that the eyes 'with prior pindolol' happened to be a relatively low pressure group compared with the SS2 eyes 'without prior pindolol,' since when the groups are compared at the time when each is actually on pindolol a difference of −3·0 mmHg is found.

Thus in these 8 patients at least it is possible to conclude that there is no evidence of a persistence of any hypotensive effect of pindolol ('follow-on' effect).

POSSIBLE 'CROSS-OVER' EFFECT

The term 'cross-over' effect refers to the possibility of pindolol drops in one eye affecting the pressure in the other eye.

Table 9 *Comparison between 'double saline' and 'single saline' pressures (all eyes)*

Right eye				*Left eye*			
SS		*S*		*SS*		*S*	
26	16	22	21	26	20	24	16
24	22	26	20	21	19	17	18
27	18	24	25	24	26	24	20
38	31	34	22	28	18	24	28
33	32	28	22	29	19	26	25
35	40	32	19	28	20	26	25
22	22	20	12	22	24	22	28
24	23	18	13	24	20	18	24
22	25	21	13	22	21	20	30
14	24	13	18	16	16	13	16
14	25	13	18	18	16	14	20
16	24	13	17	17	15	16	20
16	12	18	35	19	20	27	20
16	12	16	21	23	19	25	22
17	12	18	28	20	20	24	20
26	17	15	25	22	13	23	18
22	18	18	22	21	16	22	20
22	18	20	18	23	15	23	18
19	21	17	17	15	17	12	20
16	21	16	23	14	20	14	19
16	21	18	22	14	20	14	18
26	19	27	10	36	16	31	20
30	20	26	14	42	16	31	14
28	20	28	14	38	15	31	18
26	20	26	19	14	20	14	17
24	24	28	20	13	22	10	24
30	26	32	26	10	22	14	18
19	15	18	16	18	26	14	14
18	14	20	17	17	26	14	18
18	16	20	18	17	32	16	18
18	26	17	20	16	18	20	24
19	23	23	17	18	14	21	24
23	25	20	16	22	17	19	24
16	15	16	28	17	32	28	14
14	16	14	30	24	28	29	14
16	17	14	28	18	32	26	18

n =	72·00		72·00	n =	72·00		72·00
ϵ =	1540·00		1473·00	ϵ =	1496·00		1470·00
m=	21·38	[D = 0·92]	20·46	m=	20·78	[D = 0·37]	20·41
s =	6·05		5·61	s =	6·07		5·12
v =	36·09		31·00	v =	36·31		25·88
SE $(M_1\text{-}M_2)$	= 0·98			SE $(M_1\text{-}M_2)$	= 0·89		
t	= 0·94			t	= 0·42		
p	= NS			p	= NS		

In the comparisons made so far 'cross-over' effects have been avoided by considering only 'double-placebo' pressures. Pressures on placebo while the other eye was on pindolol have not yet been presented. Such pressures, which may conveniently be called 'single-saline' or 'single-placebo' pressures, can be compared with 'double-saline' pressures in the same eyes.

The results are set out in Table 9. It can be seen that in all the right eyes the mean of the double-saline pressures was 21·38 and the single-saline was 20·46, a

Table 10 *Pulse rates (24 patients)*

All pulses while on saline (includes pretrial pulse and pulse during SS period)			*All pulses on pindolol*
Observations (n)	= 96·00		144·00
ε	= 7215·00		10774·00
m	= 75·16	[D = 0·34]	74·82
SD	= 13·69		9·42
var	= 185·60		88·07
SEM	= 1·40		0·79
SE (M_1-M_2)	= 1·61		
t	= 0·21		
p	= NS		

difference of 0·92 favouring a possible slight cross-over effect. However, with this number of observations the difference is not statistically significant. A smaller difference but in the same direction occurs in the left eyes, the figure being 0·37. This is also not statistically significant. Thus although the figures are in favour of a small cross-over effect the point is not proved.

PULSE RATE

Table 10 shows that the mean of the pulse rates of all patients when not taking pindolol, that is, on 4 occasions, once in the pretrial examination and 3 times during the double saline period, was 75·16. The mean pulse rate during the pindolol periods, that is, on 6 occasions for each patient, was 74·82, a negligible difference of 0·34 beats per minute.

BLOOD PRESSURES

On each of the 24 patients the blood pressure was taken 4 times when no pindolol was in use, that is, at the pretrial examination and at each of the examinations during the double-saline period. The blood pressure was taken on 6 occasions while pindolol was in use, 3 times when in use in one eye and a further 3 times when it was in use in the other eye. Thus there were 96 readings taken with the patient off pindolol and 144 on pindolol (Table 11).

Table 11 *Diastolic blood pressure*

On saline			*On pindolol*
n	= 96·00		144·00
ε	= 8423·00		12783·00
m	= 87·73	[D = −1·04]	88·77
SD	= 10·91		9·33
var	= 117·94		84·377
SEM	= 1·12		0·78
		SE (M_1-M_2) = 1·86	
		t = 0·56	
		p = NS	

The means of the diastolic pressures 87·73 mmHg off pindolol and 88·77 mmHg on pindolol. The difference of −1·04 mmHg is not statistically significant.

SIDE EFFECTS

One patient complained of headaches lasting one week, but this was later found to have occurred during the double-placebo period. Another had a short period of conjunctival injection in the right eye after one week of pindolol, but the effect did not persist when the drug was continued. No other side effects were noted.

Discussion

In a previous study[3] timolol was shown to lower intraocular pressure when added to existing medication. As in the present study the degree of lowering calculated by comparing pretrial pressure with pressure on timolol was greater than the in-trial comparison of the pressure when on saline compared with the pressure when on timolol.

Such a difference could be due either to a so-called placebo effect producing a lower in-trial saline pressure or to a cross-over effect from the contralateral eye on timolol. It was not feasible to disentangle the 2 possible effects in that study, so that the validity of the various comparisons made was weakened to some degree.

In the present study, however, the introduction of a double-placebo period has enabled us to identify with much more accuracy possible placebo effects, follow-on effects, and cross-over effects. As will have been seen in the account of the results, a placebo effect of 3·79 was found (Table 1). There is no possibility of this being influenced by cross-over from the other eye, as the in-trial saline readings are all 'double saline' pressures. The existence of such a large placebo effect is of some interest and indicates the need for caution in assessing results in trials of this nature. Without the filtering out of the placebo effect (which we have achieved by ignoring pretrial readings) we would have been led into the trap of assuming a pindolol effect of 6·52 mmHg (Table 1), more than half of which would in fact have been spurious.

The exact reasons for the placebo effect are not easy to determine. One possibility in this particular type of trial is that the pretrial pressure was taken at what the patient would have regarded as a routine visit, whereas later in-trial readings would be taken at what the patient would regard as a special visit. Under such conditions he or she might be more likely to have used their other prescribed treatment more conscientiously; in other words a clinical trial improves patient compliance.

Placebo effects having been obviated, tests for follow-on effects having shown a negative result (Table 8), and cross-over effects having been avoided by comparing only double-saline pressures with pindolol, we are left with the result that pindolol undoubtedly lowered the pressure on average 2·79 mmHg when added to existing treatment.

Slowing of the pulse, effects on diastolic blood pressure, and other side effects were all negligible, so that it now seems justifiable to make further clinical trials of this drug.

Our thanks are due to Messrs Sandoz for supplies of pindolol for this trial.

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British Journal of Ophthalmology, 1982, **66**, 109–114

Cardiovascular effects of epinephrine and dipivalyl epinephrine applied topically to the eye in patients with glaucoma

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SUMMARY The cardiovascular effects of topical ophthalmological preparations of 2% epinephrine (EPI), 0·1% dipivalyl epinephrine (DPE), and placebo were studied in double-blind fashion in 20 patients with glaucoma. Both drugs and placebo produced a decrease in heart rate (2±3 beats/min) which, although small, was highly significant ($p<0·001$). Neither drug nor placebo produced a significant effect on mean or systolic blood pressure (BP) over the group as a whole ($p>0·1$). However, 5 of 20 patients responded to EPI with a significant rise in mean or systolic BP (defined as a change greater than mean change ±2 SD), whereas there were no such responses to DPE or placebo. One patient developed marked ventricular ectopy after EPI. We conclude that EPI may cause cardiovascular side effects in a high percentage of patients (25% in this study) through individual susceptibility rather than a predictable effect. DPE, a new epinephrine analogue, appears to be devoid of these effects.

Topical ophthalmic preparations are commonly employed in the treatment of patients with glaucoma. By the nature of this condition a large number of such patients fall into an older age group, a group also with a high prevalence of heart disease.

Little has been reported on the cardiovascular effects of topical eye drops. Such reports have been largely case studies, and as yet no prospective trial has been undertaken to analyse the effects of these preparations. The purpose of this study was to evaluate in a prospective, randomised, double-blind fashion the cardiovascular response to topically applied epinephrine (EPI), dipivalyl epinephrine (DPE, a new epinephrine analogue), and placebo (P) in patients with chronic open-angle glaucoma.

Patients and methods

Twenty consecutive patients with chronic open-angle glaucoma were selected as they returned for follow-up care to the Department of Ophthalmology, University of British Columbia. All gave informed, written consent. Each patient was assessed by history, physical examination, and electrocardiogram (ECG) and assigned to one of 2 groups, one with and one without heart disease.

Each patient underwent a trial of 3 different topical ophthalmic preparations on 3 separate mornings—Monday, Wednesday, and Friday. All eye drops were stopped at least 96 hours before the trial, and EPI was stopped one week prior to the trial with only oral acetazolamide being permitted to be continued. These 3 medications were supplied in coded form by Allergan Pharmaceutical Inc. with each patient's drugs individually coded and administered in randomised order to each patient. The trial was thus double-blind. The medications studied were: (1) 2% epinephrine (EPI), (2) 0·1% dipivalyl epinephrine (DPE), and (3) placebo (P). Each was administered by a physician as a single drop to each eye.

The experiments were carried out in the fasting state with patients in the sitting position. Heart rate (HR) and rhythm were assessed by a Holter ambulatory monitoring system, recording for one hour prior to administration of eye drops and for one hour following. ECGs were recorded prior to administration and 5 and 10 minutes following in order to assess

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ST-T changes. Blood pressure (BP) was recorded by sphygmomanometer in duplicate before and 1, 3, 5, and 30 minutes after medication. Blood pressure was taken by the same observer in all cases. Mean BP was calculated by the formula:

$$\text{Mean BP} = \frac{2 \times \text{diastolic} + 1 \times \text{systolic}}{3}$$

Intraocular pressure (IOP) was recorded before and 30, 60, and 120 minutes after drugs by a single observer using the Goldmann applanation tonometer. Patients were asked to report any symptoms, either systemic or local.

Each 2-hour Holter recording was analysed by Avionics Dynamic Electrocardioscanner (Model 660A). The mean HR and total number of ventricular ectopic beats (VEBs) were calculated for the 30-minute period after instituting monitoring was used to acclimatise the patients to the procedure, and the HR and VEBs counted during this period were not used for analysis.

Mean and systolic BP were analysed by comparing the values before medication (mean of 2 readings) to the mean of 2 readings taken at 3 and 5 minutes after medication. Similarly IOP was compared before and 30, 60, and 120 minutes after drug administration.

ECGs were read without knowledge of the patients by 2 members of the Division of Cardiology, and discrepancies in interpretation were settled by a third reader. Changes in ST-T segments were specifically noted.

Statistical analysis of the cardiovascular data was performed by analysis of variance nested model, with which comparisons were made between each drug in each patient group and in the 20 patients as a whole. Ophthalmological data was studied by analysis of variance of the effects of each drug at 30, 60, and 120 minutes. In analysing the IOP data one eye was randomly selected from each patient and analysis done on the IOP changes in that eye. An unpaired Student's t test was used to compare the ages of the patients in the 2 groups. Student's paired t test was used to compare the heart rate before and after drug administration in all 60 drug trials.

Results

Nine of the 20 patients were classified as having no heart disease (group A), whereas 11 were classified as having heart disease (group B). Group A was composed of 6 males and 3 females, with a mean age of 66 ± 13 (SD). Group B had 5 males and 6 females, and their mean age of 74 ± 9 was not significantly different from that of group A ($p>0{\cdot}05$).

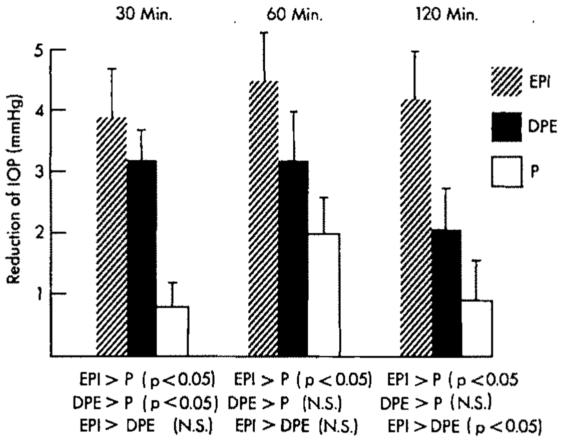

Fig. 1 *The reduction in intraocular pressure (IOP) observed after the administration of epinephrine (EPI), dipivalyl epinephrine (DPE), and placebo (P). The variations shown represent standard error of the mean.*

Of the 11 patients in group B 3 had heart disease on clinical grounds (aortic stenosis 2, raised jugular venous pressure 1). Nine had abnormal ECGs (old myocardial infarction 3, intraventricular conduction delay 4, left ventricular hypertrophy 3, and ST-T wave abnormalities 4). Fourteen of 20 patients had received EPI in the past, and 13 of the 14 had stopped the drug owing to local side effects.

All 20 patients successfully completed the study.

OPHTHALMOLOGICAL DATA

The effects of the 3 treatments on IOP was analysed in the entire 20 patients as a single block. The results comparing IOP before medication and 30, 60, and 120 minutes after medication are shown in Fig. 1.

At 30 minutes the reduction in IOP induced by EPI (3·9 ± 3·4 mmHg) was equal to that of DPE (3·2 ± 2·1 mmHg), and these were both statistically greater ($p<0{\cdot}05$) than the reduction seen with P (0·8 ± 1·9 mmHg). At 60 minutes EPI reduced IOP by 4·5 ± 3·7 mmHg, which was significantly greater ($p<0{\cdot}05$) than the effect of P (2·0 ± 3·5 mmHg) but not different ($p>0{\cdot}05$) from DPE (3·2 ± mmHg). While the effect of DPE at 60 minutes was greater than P, this difference was not significant ($p>0{\cdot}05$).

CARDIOVASCULAR DATA

Neither of the 2 medications nor placebo produced a significant change in either systolic or mean BP. The response to the preparations did not differ between the groups with or without heart disease, nor was there any difference among the 3 preparations ($p>0{\cdot}1$). These responses are shown in Fig. 2, where the changes in systolic and mean BP are shown for

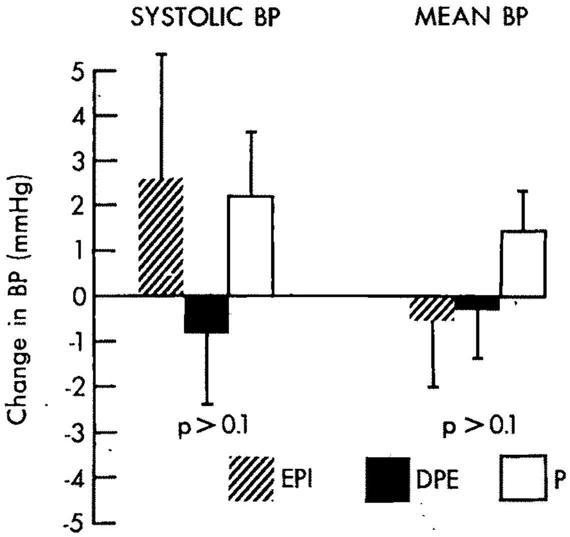

Fig. 2 *The changes in mean and systolic blood pressure (BP) seen after the instillation of epinephrine (EPI), dipivalyl epinephrine (DPE, and placebo (P). Variations shown represent standard error of the mean.*

Table 1 *Significant changes in blood pressure*

Patient	*ΔBP Systolic (mmHg)*			*ΔBP Mean (mmHg)*		
	EPI	*DPE*	*P*	*EPI*	*DPE*	*P*
1A	19*	4	0	11*	6	1
5A	21*	3	12	5	6	4
8A	17	−2	6	12*	3	3
1B	34*	5	−4	−2	0	−4
10B	21*	8	2	6	4	9

*Denotes changes in blood pressure (BP) considered to be significant (mean ΔBP ± SD).

each drug in the group of 20 patients considered as a whole. The mean changes and standard deviations in blood pressure for all 60 patient drug trials were 1·4 ± 8·5 mmHg for systolic BP and 0·2 ± 5·3 mmHg for mean BP.

Significant changes in individuals were then sought by identifying any change in systolic or mean BP greater than 2 standard deviations outside the mean change of BP. With these criteria a significant change was thus defined as a change of systolic BP of 19 mmHg or greater or a change of mean BP of 11 mmHg or greater. Four patients showed a significant change in systolic BP of 19, 21, 21, and 34 mmHg respectively. All these increases followed EPI administration; 2 were in group A and 2 in group B, the ages of the patients being 56, 74, 83, and 79. No changes in systolic BP of this magnitude were seen in any patient after DPE or P, and no major drop in systolic BP occurred. One of these 4 patients also showed a significant rise in mean BP (11 mmHg) after EPI, while one additional 56-year-old patient in group A showed an increase in mean BP of 12 mmHg, again after EPI. This individual had a rise in systolic BP of 17 mmHg, just below the level of significance in Table 1. Four of these 5 patients had previously received EPI, whereas one had never received the drug.

Mean HR showed a significant decrease regardless of the agent used. In all 60 drug administrations HR fell 2 ± 3 beats/minute from 68 ± 11 to 66 ± 10 beats/minute. While this decrease is small, it was very consistent and thus reached a high degree of significance ($p<0·001$). There were no differences among the 2 medications and placebo in their effect on HR ($p>0·05$).

Two patients in group A and 4 in group B had more than one VEB on any of their recordings. Table 2 shows the total number of VEBs from the 30-minute period before drug administration and the 30-minute period following. The numbers were too small and variable for statistical analysis, but changes in the number of VEBs appear to be important, and one patient is discussed below.

This patient was a 79-year-old male who responded dramatically to the instillation of EPI. With P and DPE he showed no change in number of VEBs per 30 minute period (6 to 2 and 1 to 1 respectively). Prior to

Table 2 *Ventricular ectopic beats (VEBs) before and after topical medication*

Patient	*Epinephrine*		*DPE*		*Placebo*	
	VEBs/30 min Before	*VEBs/30 min After*	*VEBs/30 min Before*	*VEBs/30 min After*	*VEBs/30 min Before*	*VEBs/30 min After*
5A	35	31	28	34	28	16
6A	8	11	6	9	2	5
1B*	2	362	1	1	6	2
4B	1	6	8	2	6	8
5B	14	5	305	407	167	142
7B	36	16	33	14	39	31

*Patient with a major response following epinephrine; see discussion in text and Fig. 3.

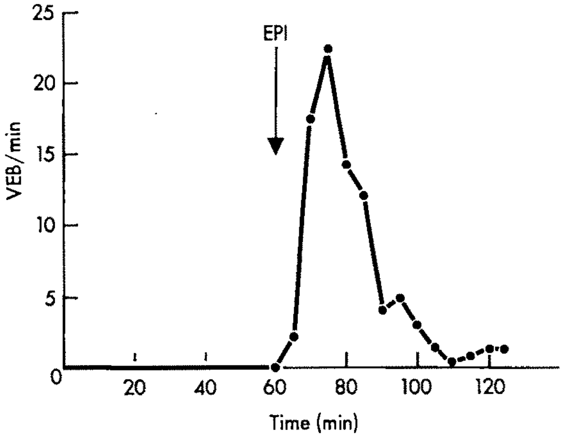

Fig. 3 *The time course of ventricular ectopic beats (VEBs) before and following the instillation of 2% epinephrine (EPI) in patient 1B (see Table 2 and text for discussion). The time of instillation of EPI is indicated by the arrow.*

EPI his Holter recording showed multiple atrial ectopic beats but only 2 VEBs per 30 minutes. Following EPI he had 362 VEBs in the first 30 minutes, beginning with 1 minute of drug administration and returning to baseline within 60 minutes (Fig. 3). His ECGs are shown in Fig. 4. This same individual also had a large increase in systolic BP (158 to 194 mmHg) after EPI but no change after DPE and P (patient 1B in Table 1). In spite of these changes he remained asymptomatic.

The reading of successive ECGs by 2 observers showed no significant change in wave form with any medication. Specifically there were no changes in ST-T waves suggesting increasing ischaemia.

No patient reported any symptoms referrable to the cardiovascular system during these studies.

Discussion

The efficacy of EPI in lowering IOP in patients with chronic open-angle glaucoma has been well established[1–4] and is thought to be due to the adrenergic effect on the ciliary body and the outflow pathways.[3–5] However, a significant number of patients on this medication for a long time develop localised side effects requiring discontinuation of the drug. These side effects include chronic irritation and hyperaemia, tearing, persistent headache, blurring of vision, and corneal oedema.[4] Hypersensitivity, blepharoconjunctivitis,[4] macular oedema in the aphakic eye,[6] and black corneal deposits[4 7 8] have been described. Becker and Morton[4] report that only 20% of patients could continue EPI for 4 to 5 years owing to the incidence and severity of these local effects.

Several reports have described systemic cardiovascular reactions to EPI. Weiner and Alvis[1] noted palpitations, tremor, sweating, and rising BP in

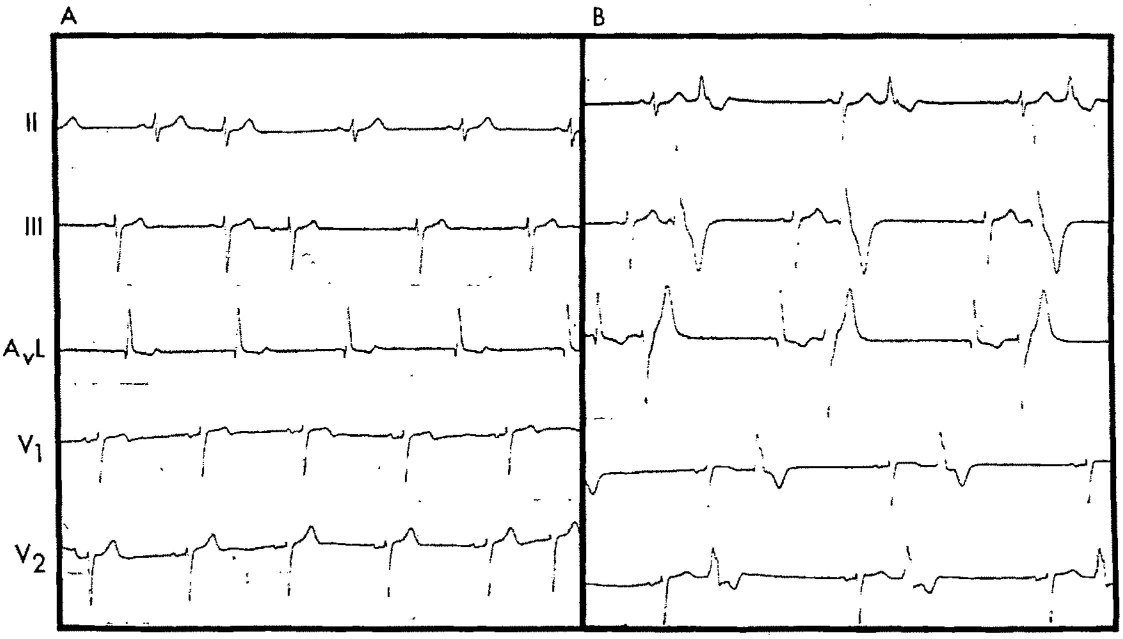

Fig. 4 *Electrocardiograms of patient 1B taken* (A) *before instillation of 2% Epinephrine (EPI) and* (B) *5 minutes following the instillation of 2% EPI. See Table 1, Fig. 3, and text for discussion.*

patients receiving both subconjunctival and topical epinephrine compounds. Becker and Morton[4] described palpitations in 4 of 50 patients receiving 2% epinephrine hydrochloride of 2% epinephrine bitartrate. Ballin[9] *et al.* showed that patients receiving EPI for a long time had more VEBs over an 8-minute period of tonography than did those receiving other medication. Becker[10] *et al.* reported at least one VEB per 4-minute period of tonography in 69% of patients receiving EPI for primary open-angle glaucoma compared with 19% of patients receiving EPI for secondary glaucoma. Both of these reports show a high incidence of isolated VEBs but do not demonstrate their occurrence in a temporal relationship to EPI administration.

Lansche[11] reported 2 cases in which 2 drops of 2% EPI resulted in transient hypertension and tachycardia lasting about 15 minutes. ECGs were not recorded during these episodes. Both cases were associated with recent incision of a chalazion or corneal epithelial disruption.

Two drops (0·05 ml/drop) of 2% EPI contain 2·0 mg of epinephrine. The usual recommended subcutaneous dose in patients with allergic reactions or asthma is 0·1 to 0·3 ml of 1:1000 solution (0·1 to 0·3 mg). Thus the doses in ophthalmological preparations are considerably higher and, if readily delivered into the circulation, might produce significant systemic effect.

DPE is dipivalyl ester of epinephrine, which, because of greater lipophilic properties, has increased absorption into the eye.[12 13] Once inside the eye DPE is hydrolysed to form EPI.[13] It has been estimated that DPE may reach concentrations in the eye about 10 times that of an equal dose of EPI without reaching significant systemic levels.[13] Thus it is possible to use smaller doses of DPE (0·1% solution) than EPI (2% solution) to obtain a similar effect. This theoretically should reduce the incidence of systemic cardiovascular side effects. DPE has been shown to lower the intraocular pressure (IOP) over a one-month period when given in a dose of 1 drop of 0·1% solution twice daily.[12]

The present study confirms the efficacy of both DPE and EPI in acutely lowering the IOP after a single administration. It would appear from our data that both have an equal effect initially, but after 60 and 120 minutes EPI is more effective in lowering IOP. It would be inappropriate to extrapolate these findings to long-term effects of these drugs. It is worth noting again that the amount of DPE used is 5% that of EPI on a purely quantitative comparison.

From a cardiovascular perspective this study has shown that neither DPE nor EPI had any statistically significant effects on BP or on the incidence of VEBs or ischaemic ECG changes. Furthermore there was no statistical difference betweeen the 2 drugs in these effects in patients with or without heart disease.

The response of the heart rate of the 2 medications as well as placebo was too slow. While this slowing was slight, it was extremely reproducible and thus attained a high degree of significance. The HR was allowed to stabilise for a minimum of 30 minutes before the baseline was recorded, and therefore a natural slowing due to progressive patient relaxation is not likely. The mechanism of this action is not clear. The fall in HR was not associated with a rise in BP, and thus a reflex bradycardia cannot be implicated. It is possible that corneal irritation as a result of local anaesthesia, tonometry, and drug administration may result in vagal discharge and thus a decrease in the rate of sinus node activity.

There was no consistent effect on either systolic or mean BP with EPI, DPE, or P. While the change in BP with EPI was more than with DPE, this was not statistically different. However, after EPI 5 patients did respond with increases in systolic and/or mean BP which are considered individually significant. These occurred only with EPI, and such increases were not seen in any patients after DPE or P. This would suggest that, while EPI does not have a predictable effect on BP, it may result in a significant increase in BP with a reasonably high frequency (25% in our study) in susceptible individuals. Three of these 5 patients had a significant increase in systolic BP but insignificant changes in mean BP. This is due to a fall in diastolic blood pressure, which, due to the weighting of diastolic pressure in the calculation of mean BP, may counterbalance the rise in systolic BP. This would explain in Fig. 2 why, although the changes in BP are not statistically significant, systolic pressure appears to increase and mean BP to decrease after EPI. These variable effects on BP may be partly explained by the mixed α and β effects of epinephrine.

Six patients had ventricular ectopy prior to instillation of drops, and as a group they showed no consistent change with medication. However, one showed a dramatic increase in the incidence of ventricular ectopic beats after EPI (as well as a major rise in BP), again suggesting a susceptibility to EPI in certain individuals. This susceptibility may represent a greater systemic absorption of the drug from the eye or it may represent an increased sensitivity to circulating epinephrine. It is not possible to differentiate these mechanisms from this study.

It is of interest that DPE showed no evidence of cardiovascular systemic reactions other than the minor decrease in HR previously described. This is in contrast to the 25% incidence of cardiovascular effects following EPI. This would support the theoretical advantage of DPE over EPI in that much lower concentrations of DPE (0·1%) than EPI

(2·0%) may be used to obtain an advantageous effect on IOP. As a consequence less catecholamine is absorbed, and thus the chance of systemic reaction is decreased. The cardiovascular side effects occurred apparently equally in the groups with and without overt heart disease, suggesting a need for caution in any patient in this older age group who might well have undiagnosable cardiovascular disease.

Several conclusions may be drawn from this study. Firstly, all topical agents in this study produced a small decrease in the heart rate, probably as a result of a nonspecific effect, possibly vagally mediated. Secondly, epinephrine may produce significant cardiovascular side effects in certain susceptible individuals, although there appears to be no uniformly predictable response. This supports previous case reports and again reasserts the need for caution in the use of topical epinephrine. Thirdly, DPE appears to be effective in lowering IOP on a short-term basis and appears to be completely devoid of systemic cardiovascular side effects. In the doses studied EPI appears to be more effective in lowering IOP than DPE after 60 minutes, possibly because of the much lower dose of DPE.

This work was supported in part by Allergan Pharmaceutical Inc., Irvine, California.

I.H. was in receipt of a Bausch and Lomb fellowship.

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British Journal of Ophthalmology, 1982, **66**, 115–117

Spontaneous cyclical pigmentary changes in a conjunctival naevus

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SUMMARY A conjunctival naevus which showed profound changes in growth and pigmentation over a period of 15 years is presented.

Spontaneous changes in the shape and size of a conjunctival naevus due to regression is very rare. Reese[1] has described the complete regression of a conjunctival naevus, but no other cases resembling this have been recorded. The following case is not one of regression, but nevertheless the pigmentary changes over the years have been sufficiently profound to be thought worth reporting.

Case report

The patient is a white male and was 13 years old when first seen in 1965. The naevus (Fig. 1) was about 2 mm from the limbus at 1 o'clock in the right eye. It was jet black with a brown halo-like area round it, widest below. About 1 mm temporal to the main mass there was a pinpoint satellite lesion. No change was noticed in May or August 1965, but by May 1966 profound changes had taken place (Fig. 2). The lesion was now T shaped and the satellite lesion had disappeared.

By June 1967 the naevus was changing its shape, and in September 1968 (Fig. 3) it looked like a brown powder with only one small black area remaining. The lower part of this area would appear to be outside the original black mass of January 1965 (Fig. 1).

This appearance was maintained until January 1971, when the patient's mother noticed a change. By

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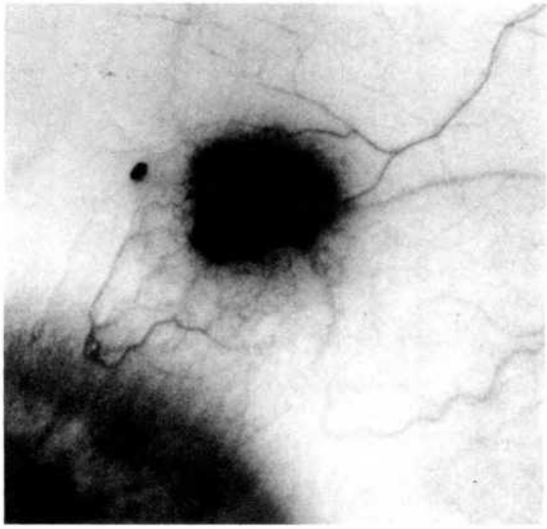

Fig. 1 *Conjunctival naevus in January 1965.*

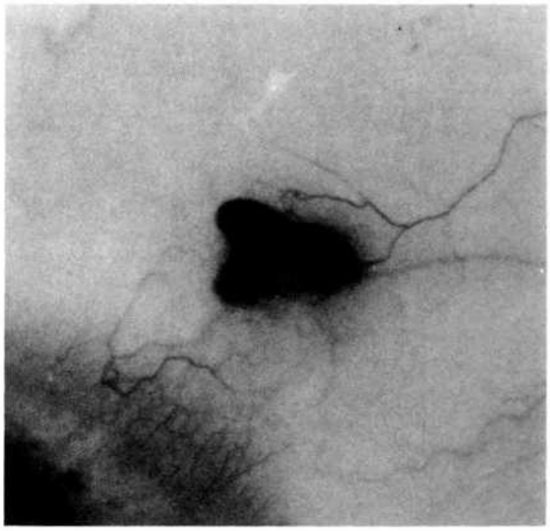

Fig. 2 *Naevus in May 1966; profound change in shape.*

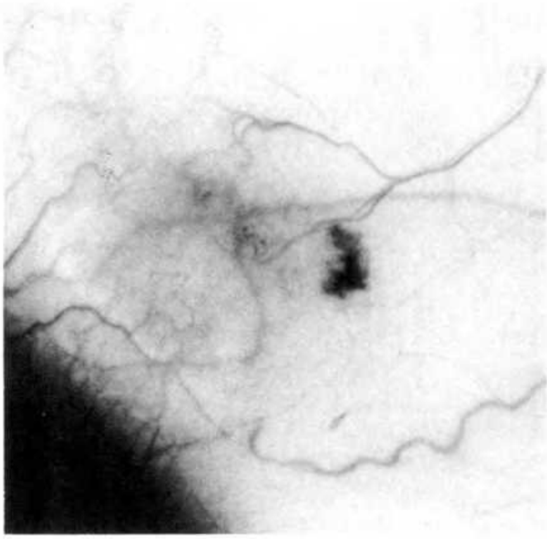

Fig. 3 *September 1968; almost complete disappearance.*

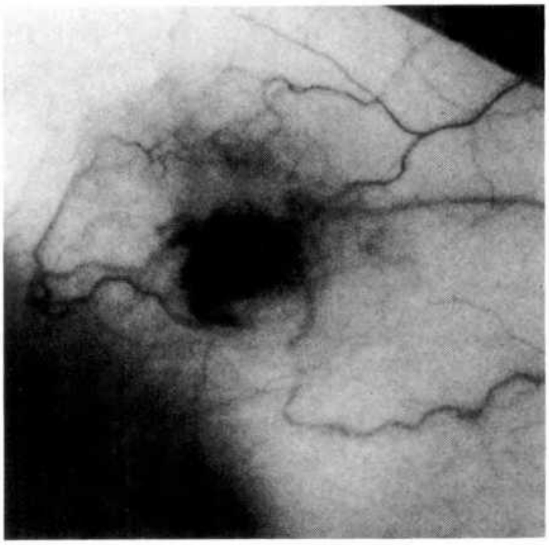

Fig. 4 *June 1971; considerable regrowth has taken place.*

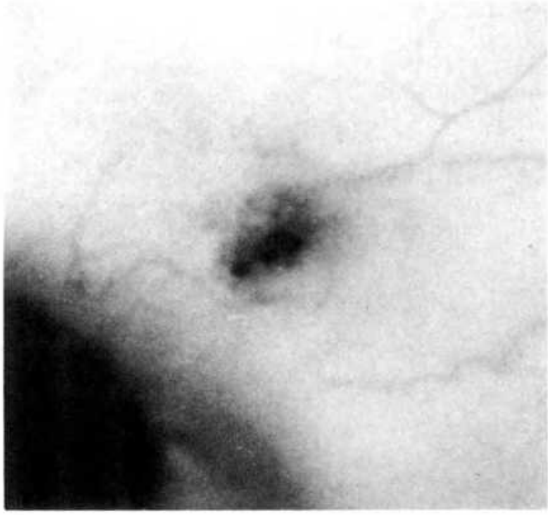

Fig. 5 *March 1976; further regression.*

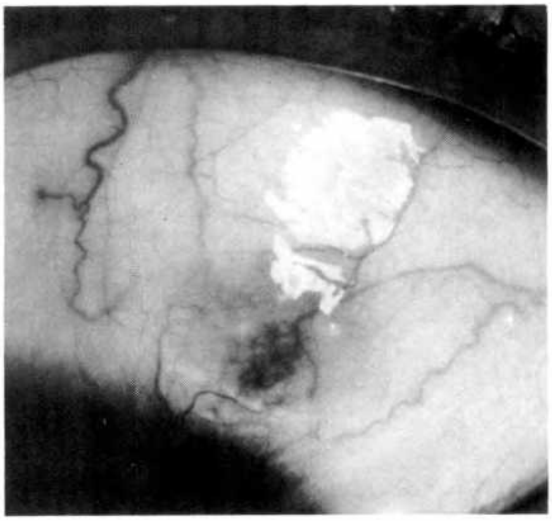

Fig. 6 *December 1980; appearance at biopsy.*

June 1971 the naevus was again quite visible (Fig. 4). This was a new area of growth temporal to the previous remaining area, which had largely disappeared.

Over the next 5 years the naevus again regressed, and in January 1976 it consisted of a few black spots arranged in a linear fashion from 8 o'clock to 2 o'clock with a surrounding brown area (Fig. 5). Subsequently, the black spots disappeared, and by December 1980 all that remained was a brown lesion of powdery appearance (Fig. 6). A small part of it was taken for biopsy.

BIOPSY

The conjunctival biopsy was a piece of membranous tissue 2 mm in diameter and light brown in colour. Paraffin sections revealed that the subepithelial tissues were packed with clumps of naeval cells and also

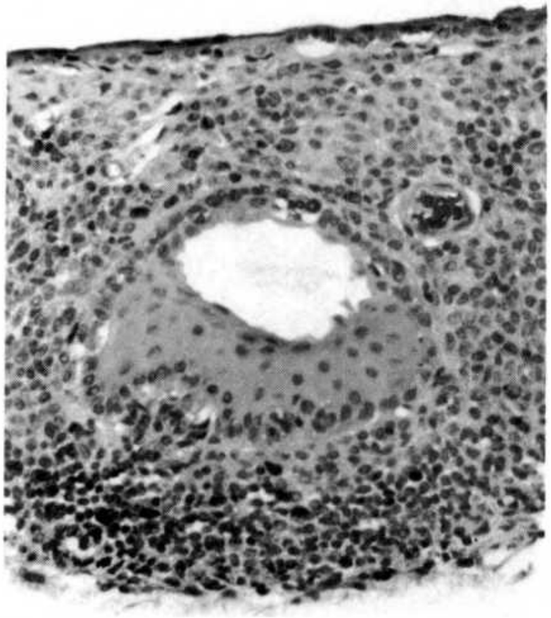

Fig. 7 *Histological appearance of biopsy specimen. (Haematoxylin and eosin, ×102).*

contained the epithelial cysts which are a feature of conjunctival naevi (Fig. 7). There were no definite junctional nests, the naeval cells all being subepithelial. In the deeper parts of the tumour the naeval cells were small, deeply staining, tightly packed, and difficult to distinguish from lymphocytes. However, it was considered that the cells were naeval cells with only a sparse infiltration of lymphocytes. Stains from melanin showed only scanty pigment present. There were no melanophages and no pigment in the epithelium. Hence the biopsy revealed a poorly pigmented subepithelial naevus with only a slight lymphocyte infiltrate.

My thanks to Dr J. Little for the histology report.

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British Journal of Ophthalmology, 1982, **66**, 118–122

Vernal keratoconjunctivitis in an Israeli group of patients and its treatment with sodium cromoglycate

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SUMMARY Vernal keratoconjunctivitis (VKC) is usually considered as an allergic eye disorder of type I, and in most therapeutic trials it has been shown to yield to topical treatment with sodium cromoglycate. This has been confirmed in the present study of VKC patients from Israel. However, some of the cases seemed not to benefit from this treatment. In a survey of IgE levels in VKC patients in Israel tear IgE levels were significantly increased in 63·5%, but in 29% of the patients both tear and blood IgE levels were normal to low. The possibility that some of the cases diagnosed as VKC might have another cause than IgE-mediated atopy is discussed.

Vernal keratoconjunctivitis (VKC) is usually considered to be an allergic, IgE-mediated disorder.[1 2] Outbreaks, exacerbations, and recurrences cluster in the spring together with hay-fever, spastic bronchitis, or asthma. A large proportion of VKC patients suffer from other atopic conditions or give a history of familial allergy. Microscopic examination of the inflammatory exudate shows consistently increased numbers of eosinophilic leucocytes. High levels of total IgE[3] and of antipollen specific IgE[4] in tears have been reported for VKC patients.

In spite of the possibility that VKC might be only one facet of a multisystem atopic condition, therapeutic trials have put emphasis on topical treatment with anti-inflammatory drugs or even by surgical correction. The topical application of corticosteroids gives considerable benefit, but it must be restricted owing to their effect on the intraocular pressure[5] or to their suppression of the defence mechanism against infections. The use of vasoconstrictors and antihistamines seems reasonable but has often proved to be ineffective, at least in severe cases.

Topical application of the nonsteroid antiallergic drug sodium cromoglycate (SCG) has been reported to be strikingly or moderately effective,[5 6–10] but a well-controlled trial from Israel[11] led to a negative evaluation of this drug. The divergent results might be due to the particular character of VKC in Israel. A comprehensive survey of patients from Israel[12] has indicated that the disease in this country is less dependent on season than has been reported elsewhere, and no connection with systemic atopy could be demonstrated. Similarly, in a report from Egypt only 5 out of 83 patients (6%) showed symptoms of other allergic conditions.[5] If this indicates that VKC in this subtropical zone is not always an allergic disorder, no effect of SCG should be expected in some of the patients. It should also be noted that in the previous Israeli study[11] a 1% solution of SCG was used, whereas other studies have been carried out with a 2% solution.

For these reasons a reappraisal of the nature of VKC in Israeli patients and of the therapeutic effect of topical SCG drops seemed to be needed.

Materials and methods

PATIENTS

Nineteen patients with VKC were treated with 2% sodium cromoglycate in a solution of 0·01% benzalkonium chloride, 0·4% phenylethyl alcohol, and water. The drops were instilled 4 times a day to one of the diseased eyes, and the fellow eye was concomitantly given a placebo solution—that is, the same preparation without SCG. No other medication was used during the observation period.

All the patients that participated were considered to have typical VKC either at their first attack or at a fresh attack after a quiescent period of the disease.

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Treatment was started in 12 out of the 19 patients during the July-August period. Only one patient had a history of another atopic condition (spastic bronchitis). Of the 19 patients 14 were males (74%) and 5 females. Seventeen were 4–10 years old, one was 12, and one 20 years old.

The eye to be treated was chosen at random by the ophthalmologist, who knew the content of the bottles, though the patients or their parents did not. Ten of the patients were admitted to hospital for control of treatment and better evaluation of its effect during the first 5–10 days. The patients or their parents were in all cases carefully told how to administer the drops and how to record the subjective symptoms (itching, photophobia, lacrimation). In spite of this the parents of 5 patients were unable to give clear information about the subjective feeling of their children. In the eye clinic the patients were subsequently examined by the same physician several times during a period of 2–8 weeks. The state and alterations of the following conditions were particularly noted and used as the basis for the evaluation of the effectiveness of the treatment: mucoid discharge, Trantas spots, epithelial keratitis, and ulceration of the cornea. The state of each symptom was graded in a scale from 0 to 3 according to severity, and it was also recorded by a drawing in the patient's journal. The compound papillary hypertrophy of the upper tarsal conjunctiva (cobblestones), a constant finding, and limbal hyaline masses which are less dynamic than the others mentioned, were not included for evaluation. Of the treated 19 eyes 6 were, according to the above symptoms, evaluated as severely, 8 as moderately, and 5 as mildly diseased. Two of the treated eyes had corneal ulcerations. Of the 19 eyes that received placebo drops 4 were graded as severely, 9 as moderately, and 6 as mildly affected; none of these eyes were ulcerated.

LABORATORY INVESTIGATIONS

Conjunctival scrapings were examined for cells and stained with Giemsa's stain. Tear samples, and in most cases also blood samples, were obtained from the patients, and examined for serum albumin and immunoglobulins. Most of these studies were performed by radial immunodiffusion as described.[13] IgE levels were determined by solid-phase radioimmunoassay (Prist, Pharmacia Ltd, Uppsala, Sweden).

Results

THERAPEUTIC TRIAL WITH SODIUM CROMOGLYCATE

Table 1 *Clinical evaluation of topical treatment with sodium cromoglycate (SCG) in 19 patients of vernal keratoconjunctivitis. One eye was treated with SCG and the fellow eye with placebo drops.*

		No. treated eyes	*No. untreated eyes*
Objective evaluation*			
Improvement	+	13	4
Questionable	±	1	2
No alteration	0	1	6
Aggravation	–	4	7
Total		19	19
Subjective evaluation†			
Improvement	+	9	6
Questionable	±	1	2
No alteration	0	1	2
Aggravation	–	3	4
No information		5	5
Total		19	19
Subjective and objective improvement‡	+/+	8 of 14	3 of 14

*The results were tested by Fisher's exact test and were statistically significant ($p<0·01$) both when the questionable cases were counted as improved and when they were counted as not improved.
†Results not significant ($p>0·1$).
‡Results at the border of statistical significance ($p=0·06$).

The overall results of the therapeutic trial with topical SCG are summarised in Table 1. The alterations in the clinical condition were fairly easy to evaluate in most cases, since improvement or aggravation was usually concordant in all the markers chosen, namely, itching, photophobia, and lacrimation for the subjective evaluation, and mucoid discharge, Trantas spots, epithelial keratitis, and corneal ulcer for the objective evaluations. The cases in which one of the symptoms was unaltered and the others improved are indicated in Table 1 as ± (questionable).

Table 1 shows a definite improvement in 13 out of 19 treated and 4 out of 19 untreated eyes according to the assessment of the objective clinical markers. If ± is counted as improved, 14 treated eyes and 6 untreated eyes were improved. The difference between treated and untreated was in both cases statistically significant ($p<0·01$) by Fisher's exact test.

According to the subjective parameters, 9 out of 14 treated and 6 out of 14 untreated eyes were reported to have improved, whereas in 5 cases no useful information was obtained. The difference here is not statistically significant. Of the 14 patients with full evaluation, 8 treated and 3 untreated eyes were improved according to both their subjective feelings and the objective observations. The significance of the difference between the treated and the placebo groups was $p=0·06$.

These results indicate a favourite effect of cromoglycate, and in some cases the rapid and clear-cut improvement after this therapy was remarkable. It should, however, be emphasised that in other patients this treatment clearly did not control the inflammatory

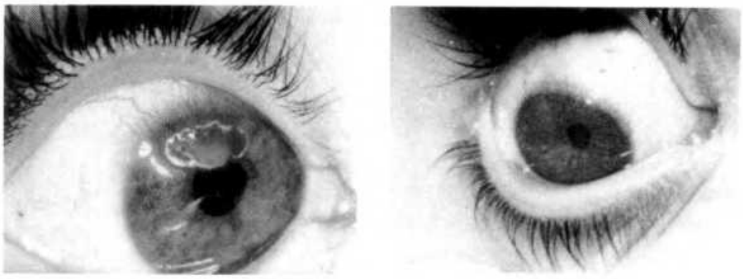

Fig. 1 *Right eye of patient, case 2. Left before, right after, treatment with SCG.*

eye disease. This difference between the patients seemed obvious, and could lead to speculation about differences in the aetiology of the disease, although the cases were clinically similar. The following observations will illustrate this point further.

Case 1

A 6-year-old boy had suffered from VKC for the last 3 years. He had severe papillary hypertrophy of the tarsal conjunctivae, epithelial keratitis of both eyes, itching, and lacrimation. Previous therapeutic trials with topical corticosteroids were unsuccessful. Conjunctival scrapings from both eyes showed a large number of neutrophilic and eosinophilic polymorphonuclear granulocytes. Treatment with SCG to the right and placebo drops to the left eye was given between 4 June and 8 August 1979. The right eye improved rapidly, whereas the condition of the left eye became worse. From August onwards SCG was prescribed for both eyes for 1½ years, but the parents reported that the treatment was not applied regularly. During this time the child experienced one severe attack of VKC and several periods with mild inflammation. Tear albumin levels were high throughout, 240–1044 mg/100 ml (2·4–10·44 g/l). The tear IgE levels exceeded by far the value for the geometric mean in healthy eyes + 2 SD (Table 2) and reached even 1237 IU/ml. The serum IgE level was 1700 IU/ml, which is also higher than the geometric mean of the control group +2SD.

Table 2 *Levels of IgE (IU/ml) in tears and blood of vernal keratoconjunctivitis patients (VKC) and healthy controls*

	Tears		*Blood*	
	Controls	*VKC*	*Controls*	*VKC*
No. samples	40	129	20	47
GM	0·92	7·88	88·92	113·63
Range	<0·42–6·6	<0·42–1350	12–485	<0·42–1700
GM + 2 SD	3·21	614·71	1024·29	2643
No. < GMC	27 (67·5%)	37 (28·6%)	10 (50%)	19 (40·4%)
No. > GMC + 2 SD*	2 (5%)	82 (63·5%)	0	4 (8·5%)

GM=Geometrical mean. GMC=Geometrical mean of control.

*The differences between the controls and VKC group were significant (p<0·001) according to the chi-square test for tears and not significant (p>0·05) for blood samples.

Levels of IgE <0·42 IU/ml could not be determined exactly. They were calculated as 0·21 IU/ml. The levels of IgE in tears from VKC patients were significantly different (p<0·01) from the levels in the control group (Student's *t* test). The corresponding difference in blood levels was at the limit of statistical significance (0·025<p<0·05). Calculation of *t* test was based on the arithmetic mean.

Comments. The immediate effect of SCG was clearly beneficial, whereas the long-term effect was difficult to evaluate, since the SCG drops were not instilled regularly. The eosinophilia observed in conjunctival scrapings as well as the abnormally high levels of tear and blood IgE may indicate that this child suffered from a type I allergic eye disease.

Case 2 (Fig. 1)

A 6-year-old boy who had suffered from VKC during the previous 2 years was twice admitted to hospital owing to the severity of the condition. He had several times had corneal ulceration of the right eye. In May 1979 he presented with a severe bilateral attack of VKC with giant tarsal papillae, diffuse epithelial keratitis and Trantas spots, and a marked corneal ulceration of the right eye. Conjunctival scrapings showed abundant eosinophilic leucocytes. The peripheral leucocyte count was $11{\cdot}9\times10^{9}$/l with 14% eosinophilic granulocytes. Treatment with SCG was applied to the right eye for 6 weeks, and the left eye was concomitantly given placebo. In the course of 3 weeks a marked improvement in the condition of the right eye was observed, and the ulceration disappeared completely, whereas no alteration in the state of the left eye was noticed. After 6 weeks the SCG treatment was extended to both eyes, and since then—1½ years—the boy has been under observation. Relatively mild recurrent attacks of the disease were observed in August 1979, April 1980, and April 1981. Tear IgE levels have been high throughout, higher than the geometric mean + 2 SD, and reached 1800 IU/ml. The IgE concentration in the blood was also high (1650 IU/ml).

Comments. The boy had already experienced several severe attacks of VKC when SCG was applied to the right eye. A raised eosinophil count in the peripheral blood and strikingly increased levels of IgE in tears and blood might indicate a type I atopic condition. SCG seemed in this patient to be clearly beneficial in the short term. It is possible that the mild nature of subsequent attacks may be due to this therapy.

Case 3

This was a 4-year-old boy with a 2-year history of VKC. The patient had previously been under treatment with topical steroids in 2 other hospitals, and had been skin-tested twice with a series of commercial allergens; all skin tests gave negative results. The patient presented on 21 August 1979 in our clinic with red, severely itching eyes, photophobia, and lacrimation. Examination of repeated conjunctival scrapings did not reveal eosinophilic leucocytes. The child was treated on the right eye with SCG and on the left eye with placebo. No essential alteration of the condition was observed in either of the eyes during the next months. The child suffered particularly on hot days ('hamsin'). During October the inflammation faded slowly in both eyes. The child was now put on SCG for both eyes during the next year and a half. New attacks were experienced in April, August, and November 1980 and April 1981. Tear levels of IgE were determined on 6 occasions and were consistently <1·75 IU/ml. Blood levels of IgE were examined on 2 occasions and were 54 IU/ml and 56 IU/ml.

Comments. In this case no indication of an allergic aetiology was obtained. Skin tests with commercial allergens were negative on 2 occasions, and no eosinophilic leucocytes were found on examination of conjunctival scrapings. IgE levels of tears were low and of blood serum below the geometrical mean of normal adults (see below). The onset of the disease did not seem to depend on the season, though hot weather perhaps aggravated it.

LEVELS OF IGE IN VKC

Table 2 shows the levels and the geometric mean of IgE levels in tears and blood of VKC patients. The control group was composed of young adults, since we have no IgE determinations on healthy children at the age of most of the VKC patients. It is of particular interest that in 63·5% of the VKC patients, the tear levels of IgE were above the geometric mean of normal persons (GMC) + 2 SD, and in 4 VKC patients the blood levels of IgE were above GMC + 2 SD. 29% of the VKC patients had tear IgE levels below GMC. All patients with tear IgE levels less than GMC, had blood IgE levels below the GMC. Of the patients with tear IgE levels greater than GMC + 2 SD 12% had blood IgE levels above the GMC + 2 SD, whereas 35% had blood levels below the GMC.

These results show that although the geometric mean of IgE levels in tears of VKC patients was far above the GM + 2 SD, a significant proportion of our patients had low IgE levels in both tears and blood. In this group the eye disorder may not be IgE mediated, and it might possibly be expected that SCG treatment of these patients would not be effective.

Discussion

VKC is usually considered to be a type I allergic disorder.[1 4 14] High IgE levels in the tears and in the blood,[3] a high proportion of pollen-specific antibody in the tear IgE,[4] a high incidence of other atopic conditions (spastic bronchitis, eczema, hay-fever, etc.) among VKC patients[8] and persistent eosinophily of conjunctival scrapings[15] are all features supporting the generally accepted opinion that VKC is a type I allergic disorder. The incidence of the disease seems to be particularly high in Israel, and especially in younger children (4–10 years old), but apparently some of its features are at variance with those reported from temperate zones. Neumann *et al.*[12] have given a comprehensive record of a group of 400 Israeli patients. It should particularly be stressed that the incidence of atopic disorders in other organs was only 11%, not more than among other children of the same age group. Likewise in a recent report from Egypt[5] the incidence of VKC patients with other atopic conditions was extremely low. Hyams *et al.*[11] have found that treatment with SCG is unsatisfactory in their patient material and have postulated that the reason might be the particular nature of VKC in the subtropical zone.

We report here a statistically verified effect of SCG treatment, and our impression from clinical observations is that SCG is beneficial in most VKC patients. However, in some patients this treatment seemed to have no effect.

This is the first study of tear and blood IgE levels in VKC patients from this geographical region. The results may indicate that the cases clinically diagnosed as VKC vary in their aetiology. In 63·5% of the patients the levels of IgE in the tears were extremely high and IgE blood levels were above GMC + 2 SD in some of the patients. Serum IgE levels above GMC + 2 SD are rare in nonatopic patients,[16] but we have not seen corresponding records of tear levels of IgE. However, in our cases the difference between the number of healthy and VKC eyes with such levels is significant. On the other hand, in 29% of the patients we found low IgE levels (below GMC) of tears and blood. It should be emphasised that in some patients with low tear IgE levels repeated examinations during recurrence of the disease showed persistently low IgE values. One example is case 3. In this child no eosinophilic leucocytes were observed in repeated conjunctival scrapings, and skin testing with commercial allergens was twice negative.

This raises the question whether the clinical diagnosis of VKC is based on a uniform pathological entity. If it is not, the rational treatment of the nonatopic patients may have to await advancement in our understanding of the real nature of their eye disorder.

We acknowledge the help of Mr David Gray, Fisons Ltd, UK, in obtaining Opticrom drops (sodium cromoglycate), and the kind help of Dr Snyder, Department of Computer Science, Bar-Ilan University, with the statistical analyses.

Mrs Judith Steinmetz has been of great help in preparing the data for publication.

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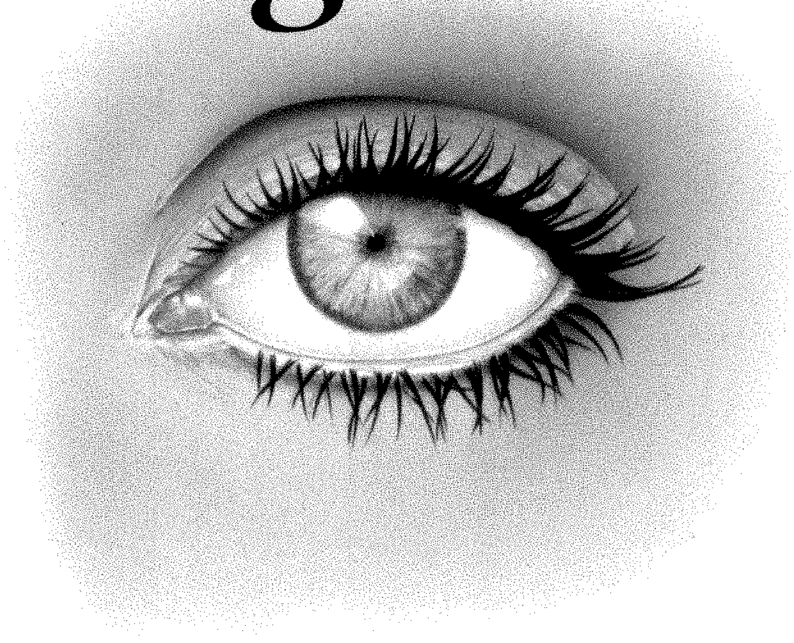

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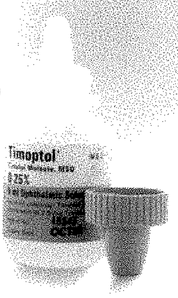

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INDICATIONS
Ophthalmic Solution 'Timoptol' (timolol maleate, MSD) is a non-selective beta-adrenoreceptor blocking agent used topically in the reduction of elevated intra-ocular pressure in various conditions including the following: patients with ocular hypertension; patients with chronic open-angle glaucoma including aphakic patients; patients with secondary glaucoma.

DOSAGE AND ADMINISTRATION
Recommended therapy is one drop 0.25% solution in the affected eye twice a day.

If clinical response is not adequate, dosage may be changed to one drop 0.5% solution in each affected eye twice a day. If needed, 'Timoptol' may be used with miotics, adrenaline or systemically-administered carbonic anhydrase inhibitors.

Intra-ocular pressure should be reassessed approximately four weeks after starting treatment because response to 'Timoptol' may take a few weeks to stabilise.

Provided that the intra-ocular pressure is maintained at satisfactory levels many patients can then be placed on once-a-day therapy. However, because of naturally occurring diurnal variations in intra-ocular pressure, satisfactory response is best determined by measuring the intra-ocular pressure at different times during the day.

Transfer from other agents
When only a single antiglaucoma agent is being used, continue the agent and add one drop of 0.25% 'Timoptol' in each affected eye twice a day. On the following day, discontinue the previous agent completely, and continue with 'Timoptol'. If a higher dosage of 'Timoptol' is required, substitute one drop of 0.5% solution in each affected eye twice a day.

When several antiglaucoma agents are being used, the patient should be assessed individually. It may be possible to discontinue some or all the other agents; adjustments should be made to one agent at a time.

Clinical trials have shown the addition of 'Timoptol' to be useful in patients who respond inadequately to maximum antiglaucoma drug therapy.

CONTRA-INDICATION
Hypersensitivity to Ophthalmic Solution 'Timoptol'.

PRECAUTIONS
Like other topically applied ophthalmic drugs, 'Timoptol' may be absorbed systemically.

'Timoptol' should be used with caution in patients with known contra-indications to systemic use of beta-adrenoreceptor blocking agents. These include bronchospastic disease, sinus bradycardia and greater than first degree heart block, cardiogenic shock, and cardiac failure. Patients with a history of severe cardiac disease should have their pulse rates checked.

Patients who are already on an oral beta-adrenergic blocking agent should be observed for a potential additive effect on either intra-ocular pressure or the known systemic effects of beta-blockade when given 'Timoptol'.

Although 'Timoptol' alone has little or no effect on pupil size, mydriasis has occasionally been reported when 'Timoptol' is given with adrenaline.

'Timoptol' has been generally well tolerated in glaucoma patients wearing conventional hard contact lenses; studies have not been conducted with patients wearing soft contact lenses.

There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenoreceptor blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Cessation of therapy involving beta-blockade should be gradual.

Use in pregnancy
'Timoptol' has not been studied in human pregnancy. The use of Ophthalmic Solution 'Timoptol' requires that the anticipated benefit be weighed against possible hazards.

Use in children
Since clinical studies in children have not been conducted, 'Timoptol' is not currently recommended for use in children.

SIDE EFFECTS
'Timoptol' is usually well tolerated.

Signs and symptoms of ocular irritation, including conjunctivitis, blepharitis, and keratitis have been reported occasionally. Visual disturbances including refractory changes (due to withdrawal of miotic therapy in some cases) have been reported infrequently.

Hypersensitivity reactions, including localised and generalised rash, and urticaria, have been reported rarely.

Aggravation or precipitation of certain cardiovascular and pulmonary disorders has been reported, presumably related to the effects of beta-blockade (see 'Precautions'). These include bradyarrhythmia, hypotension, syncope, and bronchospasm (predominantly in patients with pre-existing bronchospastic disease). In clinical trials, slight reduction of the resting heart rate in some patients (mean reduction 2.9 beats/minute, standard deviation 10.2) has been observed.

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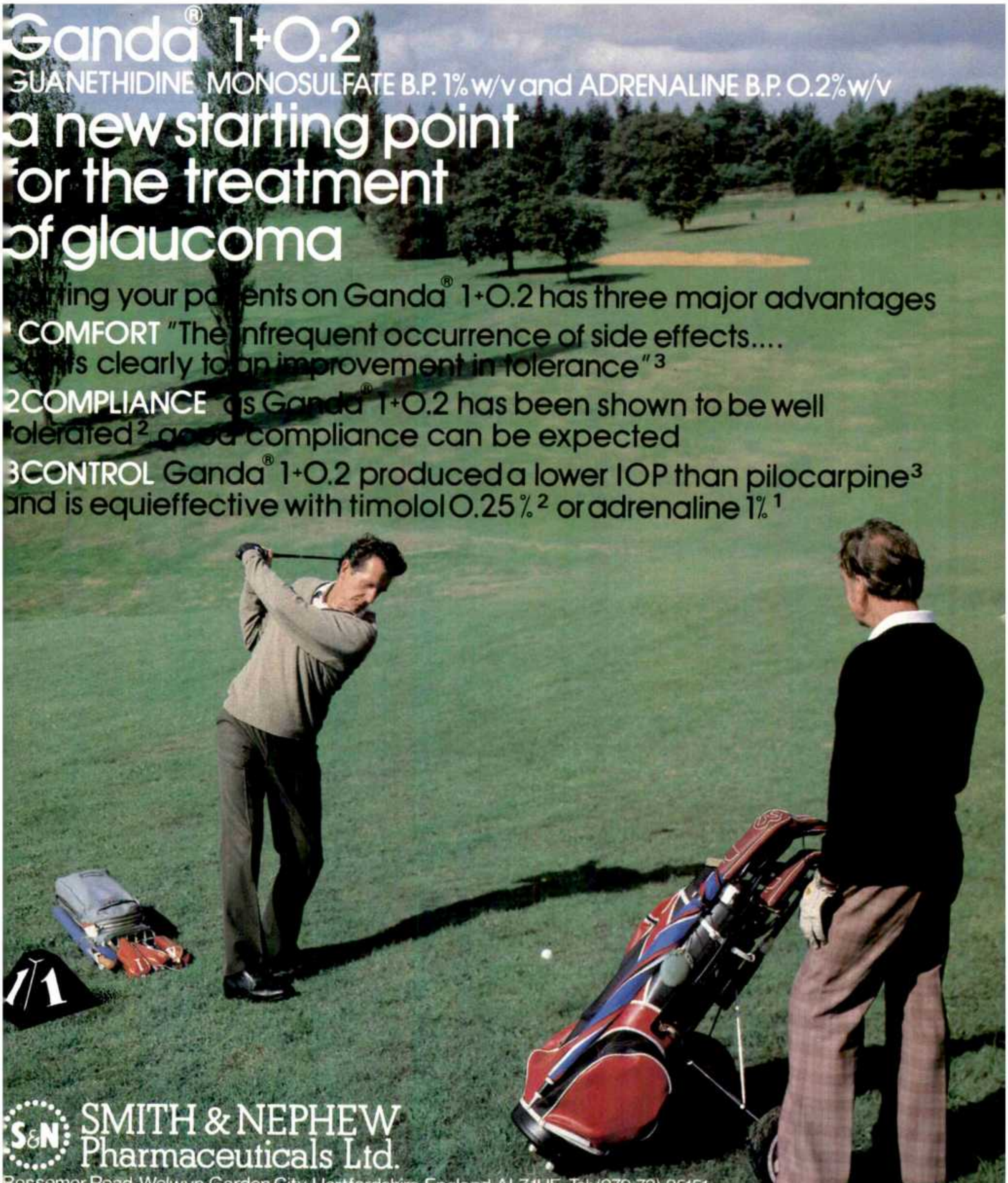

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British Journal of Ophthalmology, 1982, **66**, 123–126

Corneal sensitivity during the menstrual cycle

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*From the First Department of Ophthalmology and the *Second Department of Obstetrics and Gynaecology, University Hospital, Vienna, Austria*

SUMMARY Corneal sensitivity was determined in 5 women with regular menstrual cycles by means of a new aesthesiometer developed by Dräger. Throughout one menstrual cycle we measured corneal touch thresholds (CTT) daily and did serial determinations of urinary luteinising hormone and pregnanediol levels. CTT rose in 4 women with proved ovulation in the days before or on the day of ovulation, while corneal sensitivity remained unchanged in one anovulatory subject. We observed no changes in CTT prior to menstruation. The decrease in corneal sensitivity might be related to the preovulatory oestrogen peak.

A reduction in corneal sensitivity in the female occurs not only after operations on the eye, in various metabolic diseases, and after long-term use of contact lenses, but also in relation to physiological changes of the organism, for example during pregnancy.[1] Therefore one might assume that corneal sensitivity of the healthy eye also varies during the menstrual cycle. Millodot and Lamont described a significant reduction in corneal sensitivity in the days prior to the onset of menstruation.[2] These authors measured corneal sensitivity in 2 women daily and in 7 women at intervals of 2 weeks during the menstrual cycle by means of a Cochet-Bonnet aesthesiometer.

With the introduction of the electromagnetic aesthesiometer of Dräger a quantitative and reproducible method for the determination of corneal touch threshold (CTT) became available.[3,4] The purpose of the present study was to assess corneal touch thresholds with this new aesthesiometer during the menstrual cycle and to relate possible changes in corneal sensitivity to serial measurements of luteinising hormone and pregnanediol.

Patients and methods

Five healthy women between the ages of 21 and 35 years (mean age 26·8 years) with no eye disease and regular menstrual cycles volunteered for this study. Corneal touch threshold was assessed daily during one menstrual cycle. All examinations were performed by the same author in a separate room between 8 and 10 a.m.[5]

The electromagnetic aesthesiometer of Dräger was used in order to obtain reproducible values for corneal touch threshold.[3,4] The instrument consists of a metal tactile probe with a diameter of 0·5 mm. In order to avoid a ballistic effect the probe is approximated with nonlinear velocity. The probe touches the cornea at a right-angle under direct vision of the examiner. The pressure of the probe can be increased continuously; pressure values are shown on a digital display between 1 and 1000×10^{-5} N.

For the determination of corneal touch threshold we selected a point on the cornea at 6 o'clock 1 mm from the limbus. This point was chosen because corneal sensitivity is known to be low in the centre of the cornea, and changes in corneal sensitivity would be more difficult to prove in this area. In addition the lower part of the cornea is more accessible and usually unaffected by the patient's apprehension. Care was taken not to hold the upper lid. Originally we measured CTT on both eyes. Since the differences were not significant we evaluated CTT values from the right eye only in accordance with other studies.[6]

The actual day of ovulation was determined by serial measurements of luteinising hormone (LH). From day 10 through day 18 samples of morning urine were assayed for LH by means of the immunochemical method Hi-Gonavis.[7] To characterise the luteal phase urinary pregnanediol excretion was determined in night urine samples, and 24-hour pregnanediol excretion was calculated every other day from day 6 through day 28 of the menstrual cycle.[8]

Results

All 3 subjects with proved ovulation had CTT rises

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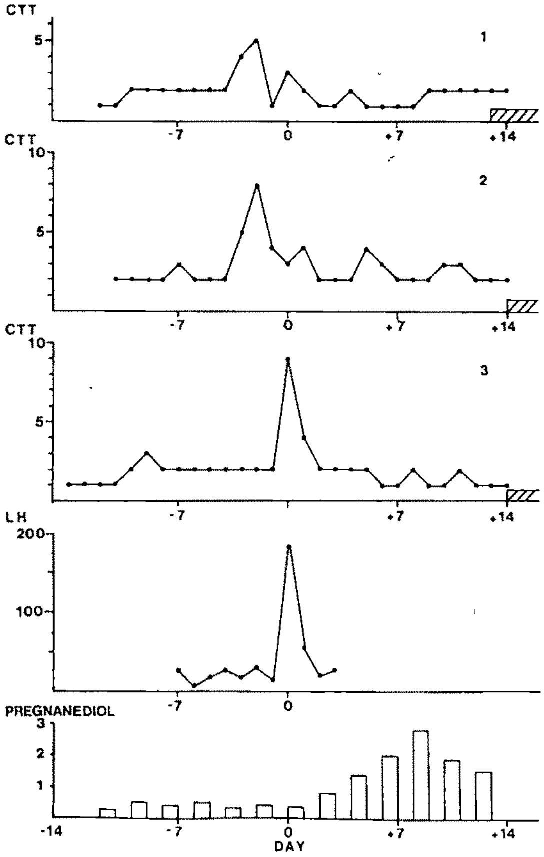

Fig. 1 *Corneal touch thresholds (CTT, ×10^{-5} N) in 3 women (cases 1, 2, 3) with proved ovulation, mean urinary luteinising hormone (LH, IU/l), and mean pregnanediol values (mg/24 h). Hatched areas indicate menstruation.*

immediately prior to (subject 1 and 2) or on the day of (subject 3) the LH peak. During the follicular and luteal phase CTT values varied between 1 and 4×10^{-5} N in all women. The periovulatory rise was at least 2-fold (subject 1), in subjects 2 and 3 even 4-fold (Fig. 1).

Subject 4 had a menstrual cycle of 29 days with no LH peak and no rise in pregnanediol excretion. This patient seemed to have an anovulatory cycle, perhaps owing to oral contraceptives taken contrary to the protocol and without our knowledge (Fig. 2).

Subject 5 had a menstrual cycle of 33 days. An LH peak was not observed, since LH measurements were discontinued on day 18. The increased pregnanediol excretion towards the end of the observation period implies ovulation around day 23–24 together with slight luteal insufficiency. Corneal touch thresholds varied between 1 and 3×10^{-5} N with a rise to 4×10^{-5} N on day 15 (Fig. 3).

Discussion

Numerous studies have been done to try to correlate ocular changes with hormonal changes during the female menstrual cycle.[26] Many investigators, however, either used instruments which did not give reproducible results or failed to characterise the

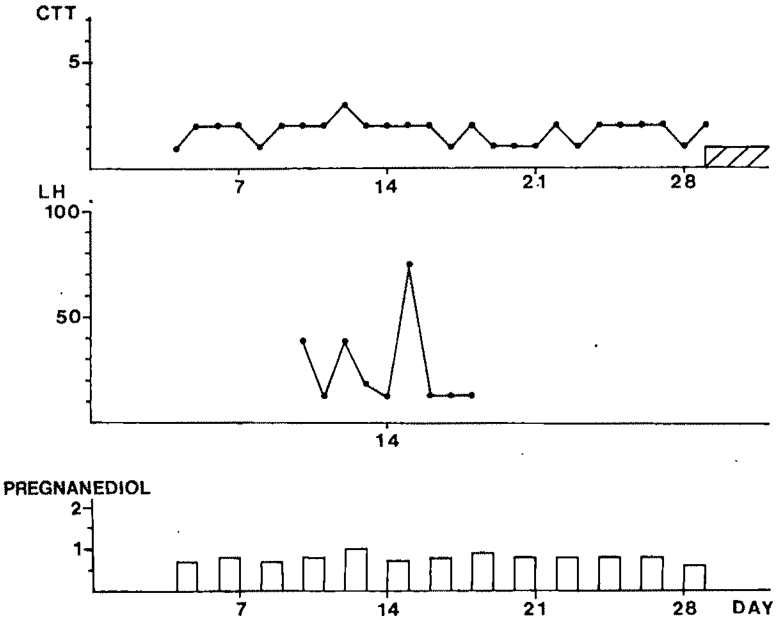

Fig. 2 *Corneal touch threshold (CTT, ×10^{-5} N), urinary luteinising hormone (LH, IU/l), and pregnanediol (mg/24 h) in relation to day of menstrual cycle in an anovulatory woman (case 4). Hatched area indicates menstruation.*

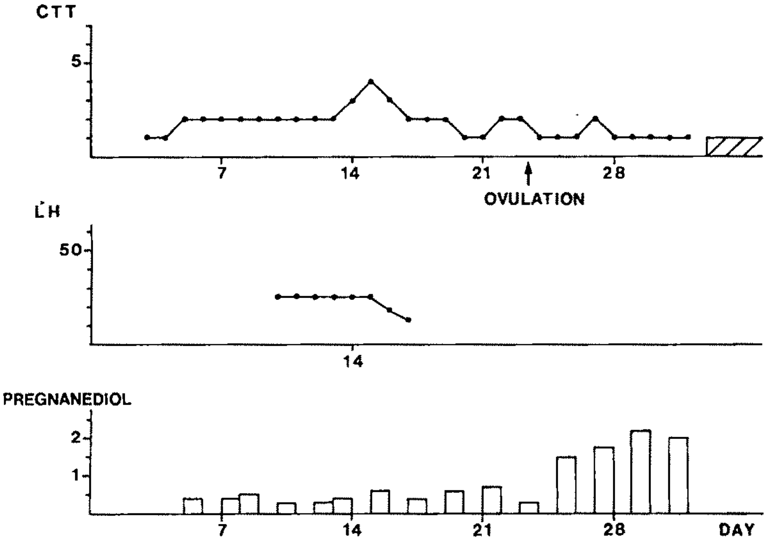

Fig. 3 *Corneal touch threshold (CTT, $\times 10^{-5}$ N), urinary luteinising hormone (LH, IU/l), and pregnanediol (mg/24 h) in case 5. Day of ovulation calculated according to the rise in pregnanediol excretion. Hatched area indicates menstruation.*

menstrual cycle adequately by means of endocrinological parameters. In a detailed study of ocular and hormonal variables throughout the menstrual cycle Feldman and coworkers[6] were unable to identify significant changes in intraocular pressure, anterior chamber depth, corneal thickness, and tear production. As for corneal sensitivity, Millodot and Lamont demonstrated a premenstrual rise in corneal touch thresholds in 2 subjects but did not prove ovulation by means of endocrinological parameters.[2]

Four of the 5 subjects in our study had ovulatory menstrual cycles of 28 to 33 days. CTT values varied between 1 and 3×10^{-5} N, with a 2- to 4-fold rise just before or on the day of ovulation in 3 women. However, in subject 5 the rise in CTT occurred 7–8 days prior to the presumed day of ovulation and was less marked than in the other subjects. One patient (subject 4) had an anovulatory cycle of 29 days; corneal touch threshold values stayed constant between 1 and 3×10^{-5} N throughout the menstrual cycle. In this cycle LH showed only a small rise on day 15, followed by a monophasic pregnanediol excretion pattern indicative of anovulation.

Our study points towards a relationship between ovulation and reduced corneal sensitivity, since all subjects with ovulatory cycles showed a reduction in corneal sensitivity a few days before or on the day of ovulation. In the subject with an anovulatory cycle (subject 4) corneal sensitivity stayed fairly constant throughout the whole cycle. However, we were unable to confirm the premenstrual rise in CTT values described by Millodot and Lamont.[2] None of our 5 subjects showed either an increase or a decrease in CTT values in the days preceding the onset of menstruation.

Since in normal menstrual cycles a significant rise in oestrogen levels is seen 2 to 3 days prior to the LH peak,[9] one might assume that this preovulatory oestrogen rise is related to the observed decrease in corneal sensitivity. In subject 5 CTT rose 9–10 days before the rise in pregnanediol excretion. This observation does not necessarily refute the hypothesis of a relationship between corneal touch threshold and the preovulatory oestrogen rise, since the menstrual cycle in subject 5 was prolonged and had a shortened luteal phase of 9–10 days. Since most cycles with luteal insufficiency are also characterised by a reduced preovulatory oestrogen rise, a possible explanation could be that in the menstrual cycle of subject 5 an immature follicle was luteinised around day 19, but a subsequent low LH peak caused only a delayed luteinisation with a delayed rise in urinary pregnanediol values.

Though our study provides some evidence for a relationship between oestrogen and corneal sensitivity, definite proof has not yet been provided. In addition it is not clear whether oestrogen has a direct effect on the eye or acts indirectly via intraocular pressure, corneal oedema, or circulatory changes in the eye. So long as the exact mechanisms responsible for changes in corneal sensitivity remain to be elucidated it will be difficult to establish a clear-cut relationship between any one parameter and corneal sensitivity.

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British Journal of Ophthalmology, 1982, **66**, 127–135

Treatment of lipid keratopathy with the argon laser

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SUMMARY Twenty-two patients with lipid keratopathy were treated with argon laser photocoagulation to the feeder vessels. Two were grafted just over a week after treatment and the corneal discs examined histologically. The remainder of the patients were followed up for at least a year. In 6 cases the visual acuity improved, in 3 deteriorated, and in 10 did not change. The density and extent of the lipid deposition were diminished in 50% of cases. The commonest complications were bleeding into the lipid keratopathy and iris damage. The only serious problem was a disciform type of lipid keratopathy that flared up after treatment. Suggestions are made on improvements in the technique of laser application.

Many patients with chronic corneal inflammatory disease are left with a vascularised scar and secondary lipid deposition. Not only is this unsightly, but it may spread across the pupil, diminishing vision and causing troublesome photophobia. Treatment may be considered under 2 main headings: primary preventive and secondary measures to deal with established disease. Primary measures include adequate early treatment of keratitis to prevent infiltration and vascularisation—for example, adequate long-term topical steroid administration in herpes simplex and zoster keratitis (with suitable antiviral cover in the former)—and the investigation and treatment of any systemic lipid anomaly. Established lipid keratopathy is more of a problem. Direct removal of superficial deposits may be attempted by keratectomy, but, when they are deeper, lamellar or penetrating corneal grafting is necessary.

Obviously the results of grafting are particularly poor in a vascularised host. Much attention has been concentrated in the past on the occlusion of these new vessels in the hope that further lipid deposition may be prevented, some resorption occur, and the host made safer for grafting. The methods have included peritomy, severing or cautery of the vessels at the limbus,[1] β radiation,[2–6] thiotepa,[7 8] and cryotherapy.[9] All these methods were assessed by Ey *et al.*[1] in the inhibition of induced vascularisation in rabbits, and they found the most effective were β radiation, thiotepa, and topical steroid. The latter is known to reduce cellular infiltration, diminish fibroplastic repair and postinflammatory vascularisation, and reduce capillary permeability associated with inflammation of the cornea.[10–12] More recently, renewed attempts have been made to occlude the new vessels unresponsive to steroid with the argon laser.[13–15] Cherry *et al.*[13] treated 4 patients with lipid keratopathy and had a short-term success in closure of new vessels in all cases, but regrowth occurred in 3 patients after 6 months. We felt that by modifying the technique used for closure of small new vessels in diabetic retinopathy[16] we might have something useful for early cases of keratopathy, further lipid deposits being prevented and existing lipid absorbed by macrophages passing into adjacent corneal lymphatics. However, in the more advanced cases we recognised that major irreversible structural changes had occurred in the cornea and that full recovery would be impossible.

We proposed to give due consideration to possible dangers to iris, lens, and retina during the trial. We decided to try to obtain the discs from patients grafted soon after corneal lasering.

Materials and methods

Patients with all degrees of lipid keratopathy were drawn on a voluntary basis from those attending the Western Ophthalmic Hospital and Moorfields Eye Hospital. A history and full examination were carried out and the following recorded: history and aetiology of keratitis, drug treatment, visual acuity, the extent, density, and vascularisation of lipid deposits, iris appearance, and lens clarity. They were reassessed every 3–6 months, and most patients were screened for any systemic lipid anomalies.

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Colour photographs were taken on the photo slit-lamp every 6 months at ×2 magnification with identical settings, lighting conditions, and film. A careful grading was made on the density and extent of lipid deposits. Density was recorded as mild, moderate, or severe, and the extent was expressed as a fraction of the total area of the cornea. Corneal fluorescein angiography was carried out on all patients prior to treatment and thereafter every 6 months to 1 year. Vascularisation was scored as mild, moderate, or severe and a note added on the size of the stem. Earlier patients were recorded at ×1 magnification on 35 mm film but later at ×2 magnification on film and videotape by the technique described by Marsh and Ford.[17] The videotape was particularly useful because it could be immediately and repeatedly replayed to identify vascular filling pattern and closure.

Prior to treatment with a coherent radiation 900 argon laser 1% amethocaine was instilled; the patient was cautioned to be very still and stare constantly at the fixation light. To a certain extent the instrument settings and technique varied and underwent evolution as we progressed. The aperture setting varied from 50 μm to 100 μm depending on the size of the vessels to be treated, but it was important to have the machine checked regularly for correct focusing of the beam. The intensity necessary to occlude the blood column varied from 0·2 to 0·8 watts and again depended on the state of repair of the machine, although we found it better to start at a low level and slowly increase. We used 0·1 s exposures, the slowest speed possible consistent with comfort. The illumination of the slit was kept as low as possible and the delivery system angled to the cornea so that rays were directed away from the pupil to the periphery of the iris. It was best to constrict the pupil prior to treatment.

We preferred to begin treatment just behind the limbus, occluding all the main feeder tracks seen on the angiograms (this tended to 'trap' blood columns in the cornea). Next we occluded the main veins, just corneal to the limbus, which expanded and darkened these columns, facilitating further photocoagulation. They were progressively closed or blackened towards the centre of the cornea. After we closed the large veins we returned to the larger arteries in which flow had been considerably slowed. Smaller aperture settings and more power were necessary to close them all along their course. We next tackled any remaining small vessels and found it best to treat them initially at 'cross-over' points and then fill in intermediate sections.

All treatments were recorded. We found it best to arrange 3 treatment sessions in a day owing to the tendency of anastomotic channels to open up ½–1 hour after initial laser treatment. So we started early in the morning, and applied the second at midday and the last in the late afternoon. In cases of profuse vascularisation patients were initially brought back for treatment every 2 weeks. As successful closure was achieved patients returned approximately every 3 months for assessment, including repeat of angiography and further treatment as necessary.

Efficacy of treatment was judged by improvement in visual acuity, a reduction in density and extent of the lipid, and by disappearance of vascularisation. Thus, these details were carefully recorded at each visit and photographed. In 2 cases histology was obtained after laser application.

Case 1 was a 27-year-old man with a history of keratitis and dense vascularised central lipid keratopathy. Photographs and angiogram were taken and laser was applied to the vessels. Ten days later a corneal penetrating graft was carried out with immediate transfer of the disc to fixative.

Case 2 was a 30-year-old man with a history of keratitis and dense vascularised central lipid keratopathy. Photographs and angiogram were taken and laser was applied to the vessels. Eleven days later a penetrating graft was carried out with immediate transfer of the disc to refrigerated fixative.

Both discs were fixed for at least 1 hour in 2·5% gluteraldehyde buffered in 0·1 M sodium cacodylate containing 10 mg/ml calcium chloride and with a final pH 7·4. After initial fixation each disc was briefly washed in cacodylate buffer containing 7·5% sucrose, and the areas exposed to laser irradiation were then isolated under a dissecting microscope. Samples of irradiated and unirradiated areas of both discs were postfixed for 1 hour in 2% osmium tetroxide in 0·2 M sodium cacodylate, dehydrated through a graded series of ethanol concentrations in water, and then embedded in Epon via epoxypropane. Semithin sections (0·75–1 μm thick) were cut on glass knives and stained with alcoholic toluidine blue.

Results

Twenty-two patients were treated with laser and of them 19 were followed up for a minimal period of a year. One patient failed follow-up after 3 months and 2 received corneal transplants 1 week after treatment.

The keratopathies could be broadly classified by morphology into several types: (*a*) central; (*b*) eccentric disciform; (*c*) marginal; (*d*) diffuse interstitial; and (*e*) diffuse deep. Table 1 shows the distribution of patients to these groups and their aetiology.

Table 2 shows the results of treatment in the 19 patients with minimum follow-up of 1 year. It can be seen that there was improvement in visual acuity in 6 cases, deterioration in 3, but no change in 10. The density of the lipid was reduced in 9 cases, increased

Table 1 *Distribution of keratopathy*

Aetiology	*Central disciform*	*Eccentric disciform*	*Marginal*	*Diffuse interstitial*	*Diffuse deep*
HS	4	5	2	1	
HZ	1	1			
Rosacea	0	1			
Trauma	0	1			
Idiopathic	0	1			2

HS=herpes simplex. HZ=herpes zoster.

in 3, but remained the same in 7. The extent of the lipid was reduced in 11, increased in 1, and there was no change in 7. Recurrence of vessels was troublesome in 7, easily handled in 4, and not a problem in 8.

COMPLICATIONS

During lasering 6 patients developed peaking of the pupil and 7 bled into the area of keratopathy. Both of these complications had usually resolved after 2 weeks and seemed not to lead to any serious long-term problems. Most patients tolerated the treatment very well, though some found fixating difficult. Occasionally, when a large vessel near the surface was treated, a hole was punched out of the overlying cornea, through which blood found its way to the surface. However, these lesions healed very well over the following days. Great care was taken to avoid hitting the iris, but it was impossible to achieve this at all times. When it was hit several reactions occurred depending on the strength and siting of the shot. Firstly, nothing appeared to happen; secondly, a sudden spurt of cells and debris appeared in the adjacent aqueous drifting upwards, often accompanied by the production of an air bubble on the iris and a faint popping sound. If a major radial artery to the sphincter was hit peaking occurred.

The commonest late complication occurring in nearly all cases was iris atrophy. This obviously lay under the treated area and was chiefly stromal. The pigment epithelium was visibly breached in a few cases only. In 2 the pupil was permanently peaked. These complications rarely gave rise to a visual or cosmetic problem. There was no biomicroscopically observable lens defect as a result of treatment in any of the cases (the longest follow-up period being 5 years). So far as we are aware, the retina was not

Table 2 *Results of laser therapy in 19 cases of lipid keratopathy*

Case	*Distribution of lipid*	*Density*	*Extent of cornea*	*Vascularity*	*Stem*	*Amounts of laser (sittings)*	*Density*	*Extent*	*Visual acuity (Snellen's)*	*Vascularity*
1	Marginal	Mild	1/9	Mild	Several	114 (2)	Less	Less	Same	A little recurrence
2	Marginal graft host junction	Moderate	1/10	Moderate	Narrow	1154 (3)	Much less	Much less	Same	No recurrence (Fig. 1)
3	Graft host junction	Moderate	1/8	Moderate	Narrow	868 (3)	Less	Same	Same	Minimal recurrence
4	Eccentric disciform	Severe	1/3	Moderate	Several	4023 (14)	Less	Less	Same	Constant recurrence
5	Eccentric disciform	Severe	1/2	Moderate	Multiple	2411 (5)	Same	Same	Same	Constant recurrence
6	Failed follow-up at 3 months									
7	Eccentric disciform	Moderate	1/4	Profuse	Broad	891 (1)	Less	Less	Same	Some recurrence
8	Eccentric disciform	Moderate	1/6	Mild	Narrow	68 (2)	Much less	Much less	Improved	Minimal recurrence (Fig. 2)
9	Eccentric disciform	Moderate	1/2	Moderate	Narrow	859 (3)	Much less	Much less	Improved	Minimal recurrence
10	Eccentric disciform	Severe	1/4	Moderate	Narrow	577 (2)	Same	Same	Same	Some recurrence
11	Eccentric disciform	Severe	1/4	Moderate	Several	2562 (4)	Same	Less	Slightly improved	Minimal recurrence
12	Eccentric disciform	Severe	1/3	Moderate	Several	2180 (4)	Slightly less	Less	Same	Minimal recurrence
13	Central disciform	Moderate	1/4	Moderate	Multiple	9417 (14)	Worse	Worse	Worse	Constant recurrence
14	Central disciform	Severe	1/4	Moderate	Narrow	331 (2)	Worse	Same	Same	Constant recurrence
15	Central disciform	Severe	1/6	Moderate	Several	1865 (3)	Same	Less	Same	Minimal recurrence
16	Central disciform	Severe	1/3	Profuse	Narrow	2592 (5)	Worse	Same	Worse	Constant recurrence
17	Central disciform	Moderate	1/6	Moderate	Multiple	3302 (7)	Same	Less	Worse	Some recurrence
18	Deep diffuse	Mild	1/4	Moderate	Narrow	704 (4)	Same	Same	Better	Some recurrence
19	Deep diffuse	Mild	1/4	Profuse	Narrow	2791 (5)	Same	Same	Better	Some recurrence
20	Superficial diffuse	Severe	1/2	Profuse	Multiple	9889 (13)	Much less	Less	Better	Constant recurrence

struck, though this was difficult to assess in some patients with dense opacities.

Two cases got obviously worse after treatment, and both were severe disciform types. The first, however, lost most of his vascularisation and was successfully grafted after 3 years. The second, unfortunately, developed a very serious disciform keratitis. This was partly accounted for by his failure to take his steroid drops after treatment, and his scarring became very dense.

HISTOPATHOLOGY

Both cases showed a similar distribution of vessels in the peripheral cornea with the anterior two-thirds of the stroma predominantly involved. Also in both patients the stromal lamellae were irregular, and centrally a marked erosion of this layer had occurred, resulting in a total central corneal thickness in case 1 of only 280 μm. Descemet's membrane was abnormally thick for individuals in their late 20s, and in some areas discrete deposits of lipid were observed within this structure close to its anterior surface (Fig. 1e, f). The endothelium in these specimens appeared relatively normal, but macrophages were often observed in contact with its aqueous aspect.

The interpretation of the irradiated areas is complicated by the secondary tissue reactions that have occurred during the postexposure periods. The most significant changes were observed in the more superficial layers of the stroma. The topography of the damage would suggest a highly localised primary damage site associated with limited heat flow from the vessels that absorbed laser irradiation. However, the lamellar structure of the stroma, with vast regions of extracellular collagen, results in an amplification of secondary tissue responses, with tissue displacement through the presence of oedema and macrophages.

Two types of reaction were seen associated with blood vessels in the superficial stroma, namely, haemorrhages (Fig. 2) and blood stasis in areas of capillary closure (Fig. 2). Many areas of haemorrhages were observed, and these were presumably coincident with certain areas of irradiation. The haemorrhages were of various sizes, and haemolysing red blood cells could often be seen in the abnormally distended spaces between adjacent lamellae. Blood cells were particularly prominent in the region of Bowman's membrane and were often found between this layer and the basal cells of the epithelium. In many areas the disruptive effects of blood cells, macrophages, and oedema had resulted in gross distortions of the regular array of the basal cells such that they resembled those in the limbus (Fig. 3). In other areas the distortion was so gross that islands of epithelial cells were observed deep within the stroma, and some were undergoing division here.

Only 2 areas were found with incompletely healed epithelial erosions, which suggested that significant bleeding to the surface of this cornea was rare and that most sites were repaired within 10 days of exposure.

Vessels showing blood stasis with haemolysing blood cells and areas of capillary closure were usually less superficial and did not have changes in the adjacent tissues that would suggest that they were sites of irradiation. These changes in deeper vessels were probably due to interrupted flow in feeder or drainage systems. Many of these vessels were surrounded by macrophages and were abnormally swollen, both of which reactions caused further distortion of the adjacent lamellae.

In all areas where oedema and macrophages were present, but especially in the superficial layers, active keratocytes were also observed, and most of these had the rounded appearance of embryonic cells.

Discussion

We achieved some success in reducing the extent and density of the keratopathies. As expected, the early milder and marginal cases did best. The very advanced central types were devascularised, however, and made easier for grafting. We were very heartened by the one diffuse dense superficial keratitis which improved considerably. Aside from the small number

Fig. 1a, b *Preoperative photograph and angiogram of patient 2 with lipid deposit at graft host junction.* c, d *Postlaser photograph and angiogram of patient 2 one year later.* e, f *Light micrograph of central cornea showing erosion of stroma and the presence of both neovascular complexes and lipid deposits. The marker is 100 μm. High-power light micrograph of the posterior cornea in 1e showing lipid deposits within Descemet's membrane and a macrograph in contact with the endothelium. The marker is 10 μm.*

Fig. 2a, b *Preoperative photograph and angiogram of patient 7 with lipid deposition in eccentric disciform keratitis.* c, d *Postlaser photograph and angiogram of patient 7 one year later.* e *Light micrograph of the anterior cornea showing the presence of red blood cells within the stroma resulting from small haemorrhages, and red cell packing in non perfused vessels (arrowed). The marker is 50 μm.*

Fig. 3a, b *Light micrograph of anterior cornea showing distortion of Bowman's membrane and the presence of numerous red blood cells trapped between the stromal lamellae. Light micrographs of both an occluded (arrowed) and* (c) *reopened (arrowed) vessel in case 1, both showing the presence of red blood cells between the lamellae of the adjacent stroma. The marker is 25 μm.*

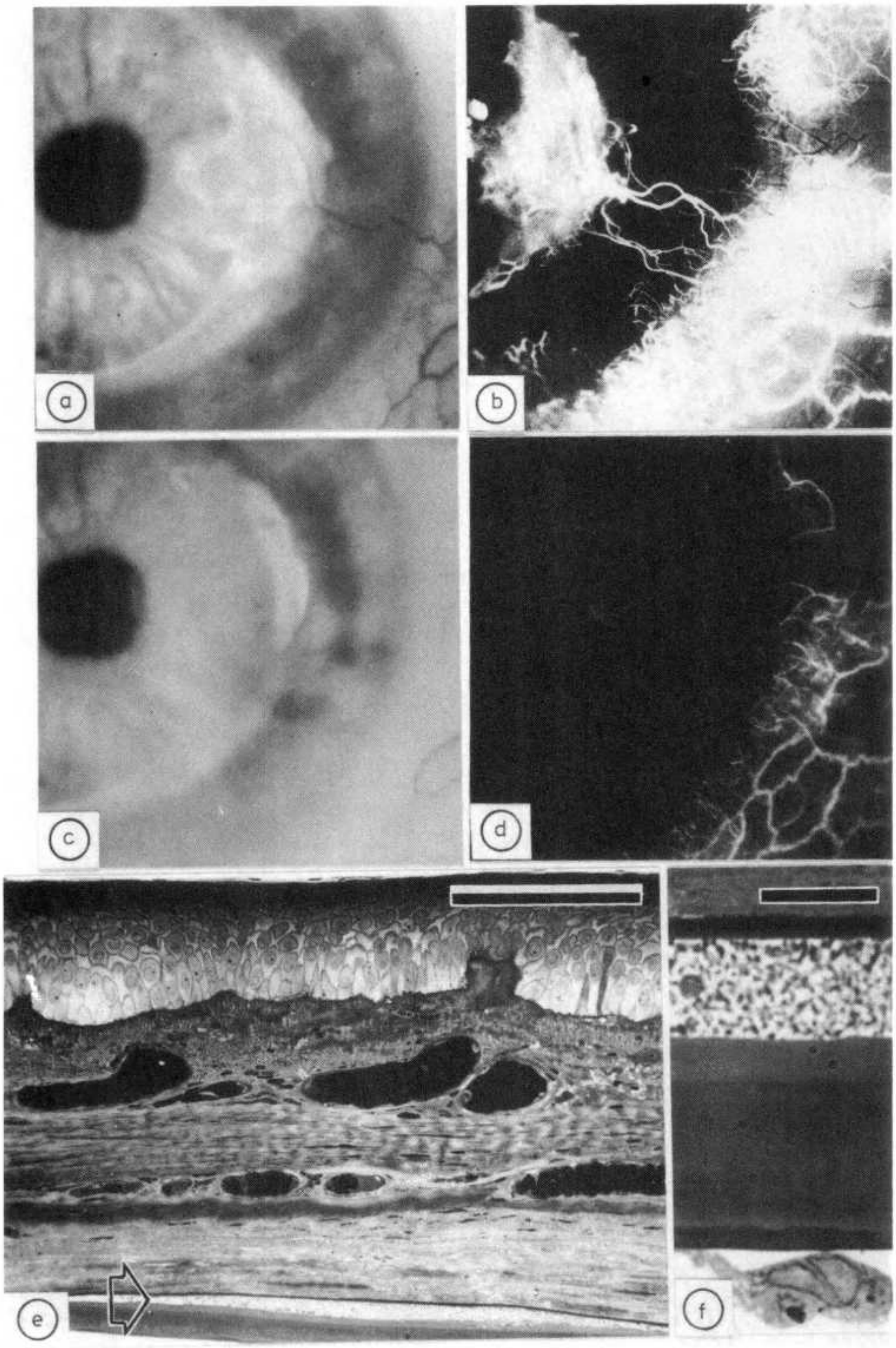

Fig. 1

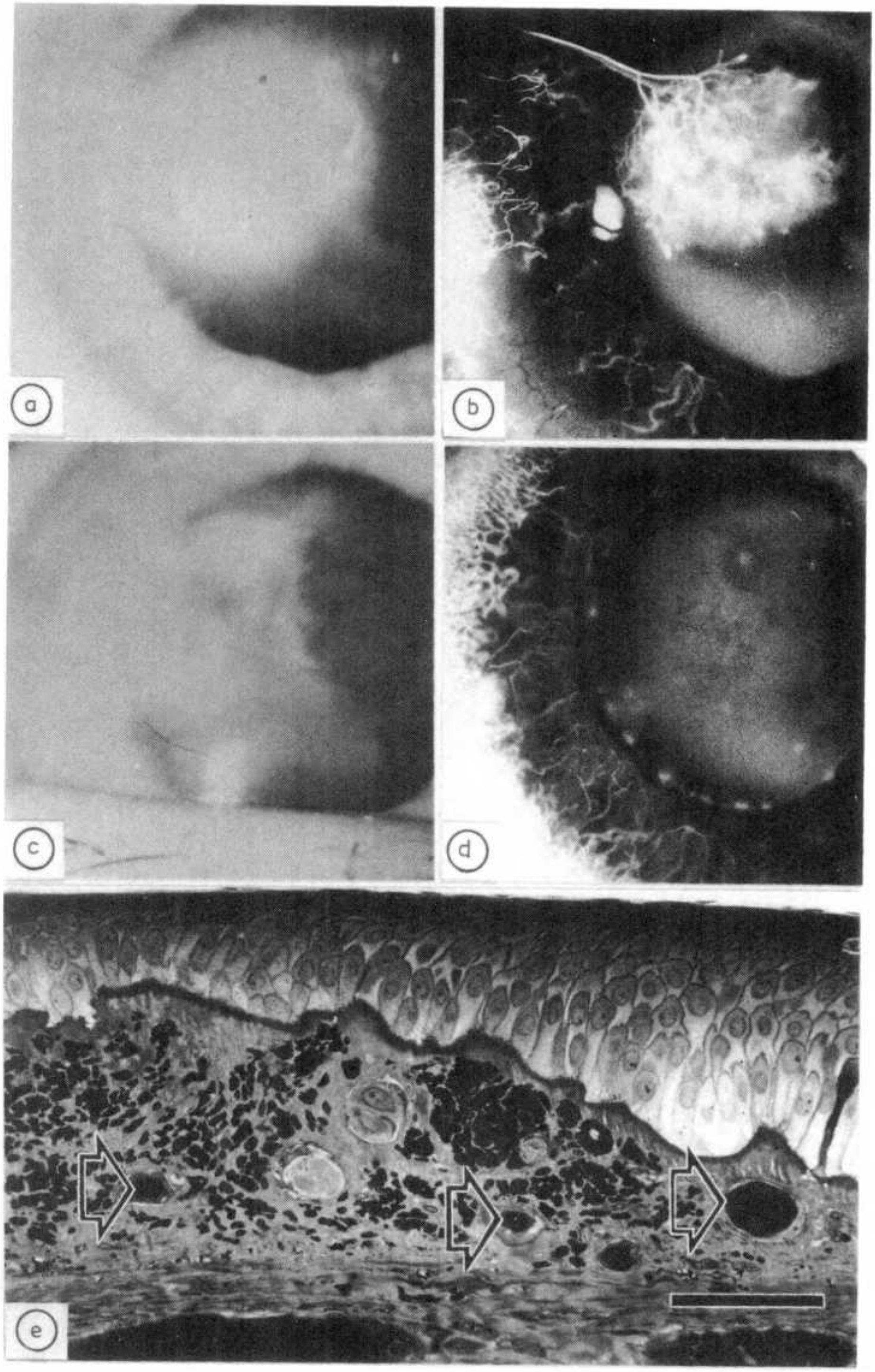

Fig. 2

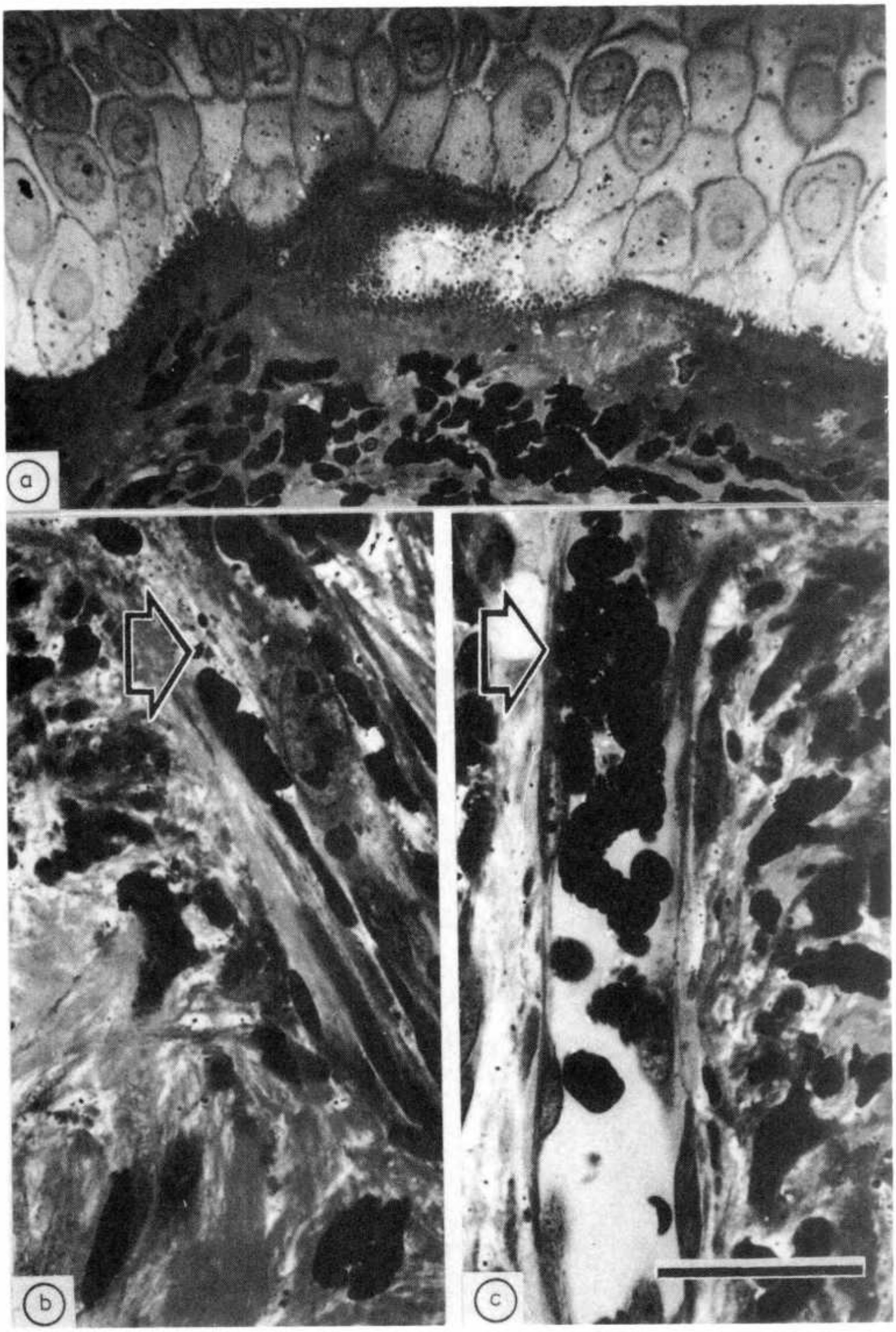

Fig. 3

of cases with improved Snellen's visual acuity many were subjectively better and their symptoms of photophobia improved. It is also notable that a large number failed to progress, contrary to the normal natural history.

The mechanisms of laser-induced vascular occlusion are not fully understood, and elucidation of this problem was not an objective of the present investigation. However, in general our observations support the conclusions drawn from similar studies on argon laser irradiation of retinal vessels.[18] In essence, whatever the secondary mechanisms of vessel closure, they are dependent upon absorption and degradation of laser energy by haemoglobin. The focal irradiance on the vessels must be high to deposit sufficient energy within them to achieve damaging thermal profiles at the vessel wall. Thus attempts to close capillaries with 120 μm spot size exposures were always unsuccessful, because the area absorbing was always too small a portion of the total area irradiated. Once sufficient energy had been deposited within an irradiated vessel to induce temporary blood stasis further coagulation became relatively easier, because the cooling effect of flowing blood was lost. However, we found in our study, as in previous investigations, capillaries remained patent in areas of irradiation even when extensive necrosis of the capillary wall had occurred. Moreover evidence of intracapillary thrombosis and true fibrin deposition was rare, while small haemorrhages were common. Until detailed investigations of thermally induced occlusive processes are undertaken to optimise the required effect such surgical procedures remain empirical and depend upon the experience of the surgeon.

We are clearly concerned about the complications. Corneal transmission of short argon lines of emission is poor; thus dissipation in the cornea may be harmful.[19] The human iris appears to be fairly resilient, and the commonest side effect is a temporary rise in intraocular pressure, with minimal disturbance of the blood/aqueous barrier.[20] We found it important to suppress the postlaser inflammatory response with topical steroid and to continue a low maintenance dose to suppress reopening of vessels. However, the iris is so close to the lens that transmission of heat from iris tissue to the lens is readily made.[21] The lens becomes progressively pigmented with aging; thus there is an increase in absorption at short wavelengths and a greater potential for the dissipation of heat here.[22] The retina may be damaged by 2 means: either an accidental direct burn, which should not occur if the beam is accurately directed; or by repetitive exposure to blue light, which has been shown to cause damage in animal eyes.[23] The complications seem to be acceptable in the short-term barring the severe iris damage, but our follow-up had to be carefully supervised, and multiple applications and visits were necessary in the very vascular lesions.

We can make suggestions on improvements in the technique so that there is added safety. The first is to make a very short focal length to the treatment beam by introducing a convex lens in front of the mirror of the slit-lamp to cause a widely diverging beam to develop after the point of focus, thereby decreasing the irradiance at deeper tissues. (Recently a new contact lens has become available for better lasering of lipid keratopathy. It is an Abraham lens, provided by Coherent Incorporated, UK. It is basically a scleral contact lens with an added strong convex lens cemented to its surface in one quadrant. It has an antireflective coating. The convex lens makes it possible to achieve a more convergent beam and thus avoid excessive iris damage. The contact lens also provides facilities for steadying the eye during treatment. We have found it extremely easy to use.) Secondly, the cornea, lens, iris, and retina absorb more light at short wavelengths; possibly it would be better to use a blue dye for delineating the vessels and a red laser to occlude them.

What is required now is a carefully controlled long-term study. We have started such an investigation with random allocation of cases to 3 groups: (*a*) has orally administered candicin; (*b*) has laser treatment only; and (*c*) has combined candicin and laser treatment.

We thank the surgeons at Moorfields Eye Hospital and the Western Ophthalmic Hospital for referring their cases. It is a pleasure to thank Mr P. West for technical help and Miss C. Smyth for secretarial assistance.

We are grateful to both the Muirhead Trust and the British National Committee for the Prevention of Blindness for the purchase of our light microscope and accessories.

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British Journal of Ophthalmology, 1982, **66**, 136–140

Assessment and interpretation of corneal endothelial cell morphology and function following cryopreservation

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SUMMARY Scanning electron microscopy, specular microscopy, and staining techniques were used in a short-term study of the standard method of cryopreservation. Correlation of the techniques revealed that the endothelium had an atypical morphology, showed apparent evidence of latent cell damage, and lacked function.

A successful and simple technique for corneal cryopreservation continues to hold out the hope for indefinite storage and easy transport over long distances. It would enable setting up a tissue bank which could be used for the close matching of donor and recipient by typing techniques[1 2] and allow the use of tissue in regions where donor material is unavailable. Early investigations of preservation techniques[3–6] have led to the development of the present clinical method.[7] The studies employed vital staining, endothelial culture, and keratoplasty in animals to assess survival and function. Specular microscopy[8 9] and scanning electron microscopy[10] were not employed at this initial stage, but more recently there have been reports of the appearance of the endothelium in preserved tissue using transmission and scanning electron microscopy.[11–13]

The purpose of this report is to describe morphological changes in the endothelium of cryopreserved corneae using specular microscopy and scanning electron microscopy. Endothelial function is also to be assessed by the measurement of corneal thickness maintenance in a perfusion system.

Materials and methods

Dutch rabbits were killed with pentobarbitone. The eyes were immediately enucleated and precooled to +4°C along with the preservation solutions of dimethyl sulphoxide and sucrose in albumin or serum. Freezing to −196°C and thawing were carried out according to the method of Capella and Kaufman[7] by the prescribed cooling box,[14] or by a method designed to reduce mechanical trauma. In the second method corneae were mounted on specular microscopy rings and frozen endothelium-side-up in 5 ml solution in plastic scintillation vials. Freezing and thawing profiles were suitably adjusted for the different thermal properties of the plastic vial. Any subsequent staining or fixation procedure was undertaken with the corneae still mounted.

Nitroblue tetrazolium was used to demonstrate viable cells after 3 hours incubation. After fixation for scanning electron microscopy (SEM) with glutaraldehyde and osmium tetraoxide[10] the specimens were viewed at 9·5 kV on a Cambridge S4 microscope. Post-thaw incubation prior to SEM was carried out at 35°C in glutathione bicarbonate ringer (GBR at pH 7·4).[15] This solution was also used for perfusion of mounted cornea on the specular microscope. Specular microscopy was used to assess corneal function by serial thickness measurements. The average of 3 readings from endothelium to the stromal/epithelium interface was taken. The microscope was also used to assess cell morphology.

Results

Immediately after the freeze/thaw cycle nitroblue tetrazolium staining demonstrated, at best, 70% endothelial survival as shown by dye precipitation resulting from retention of normal intracellular oxidative enzymes.

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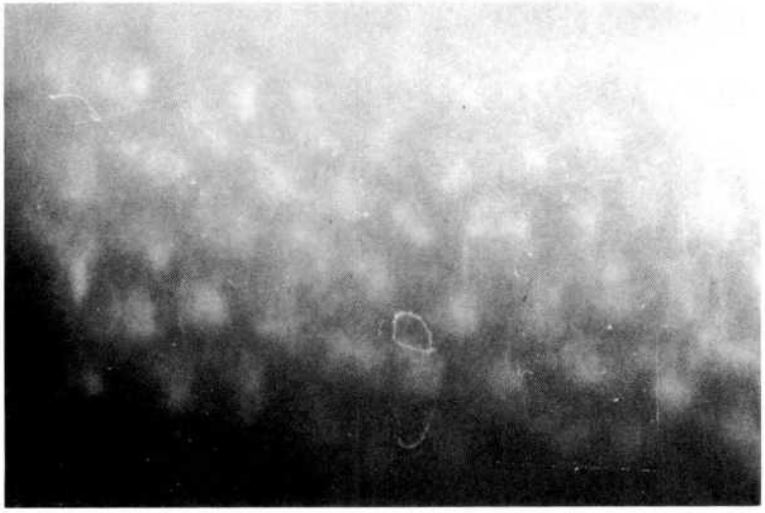

Fig. 1 *Specular image immediately after the freeze/thaw cycle (×570).*

Specular microscopy in normal corneae showed an initially darkened cell layer, which with the passage of time lightened and lost granularity as the cell margins became more distinct. The normal polygonal appearance was retained for over 6 hours after which the cells darkened and the cornea became cloudy.

When corneae were treated with the preserving solutions without freezing only slight morphological change occurred. The cells darkened and became slightly granular. Occasional dark dots made transient appearances along the cell margins. Specular microscopy immediately after thawing frozen tissue showed the endothelium as a dark field with granular central bright areas approximately half the size of a normal cell (Fig. 1). Cloudiness of the stroma made it difficult to view late cellular changes. The majority of the bright areas enlarged within the first 10 minutes of perfusion and small bright bodies occurred, apparently, in the cell cytoplasm. Examination of the central cornea revealed an occasional dark zone the size of a single cell. Clarity was gradually reduced and few preparations allowed examination after 2 hours.

Morphological examination of untreated control corneae with the SEM presented a regular array of polygonal endothelial cells with sharply defined, interdigitating cell borders. The surface was relatively smooth except for small particles. This image was still evident after 6 hours of perfusion (Fig. 2a). Immediately after the freeze/thaw cycle SEM revealed a generalised cell surface pitting (Fig. 2b). In contrast to the controls there were no obvious cell junctions. The cellular nature could be distinguished by the apparently prominent nuclei. Tissue fixed 3 hours after perfusion revealed gross changes in a small proportion of cells. Isolated cells had ruptured and detached from the cell layer. After 6 hours perfusion there was general disruption of the cell layer (Fig. 2c). The cells had rounded and drawn back from each other, remaining joined only by thin bridges. There was surface pitting with many surface fenestrations.

Serial measurements of corneal thickness were plotted graphically to give a dynamic representation of endothelial function. When controlled corneae were removed from +4°C on this system, after a lag period thinning occurred at a rate of 20 mm $\times 10^{-3}$ h^{-1}. A normal thickness of 380 to 400 mm $\times 10^{-3}$ was achieved and maintained. Thickness maintenance continued for at least 6 hours after mounting. Nonfrozen cryoprotective treated corneae gave atypical maintenance thickness curves (Fig. 3). Thickness maintenance eventually occurred but usually at a higher than normal thickness. Freeze/thaw corneae were initially thin (325 mm $\times 10^{-3}$) owing to the hyperosmotic nature of the preservatives. Thickness increased at a rate of at least 200 mm $\times 10^{-3}$ h^{-1} until clarity was lost (Fig. 4). Both frozen and nonfrozen (in GBR) 'stromal' preparations, where the epithelium and endothelium had been removed, increased in thickness at a rate of 800 mm $\times 10^{-3}$ h^{-1} on perfusion (Fig. 4).

Discussion

We deduce from this study that during incubation after the freeze/thaw cycle there was a gross disturbance of the endothelial monolayer. The morphological changes were observed with both the specular and scanning electron microscopes. Functional assessment of corneae with the specular microscope by thickness measurement showed that there was a

Fig. 2a

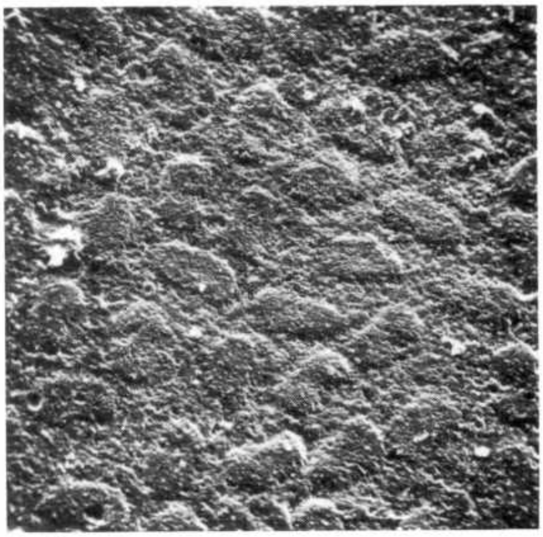

Fig. 2b

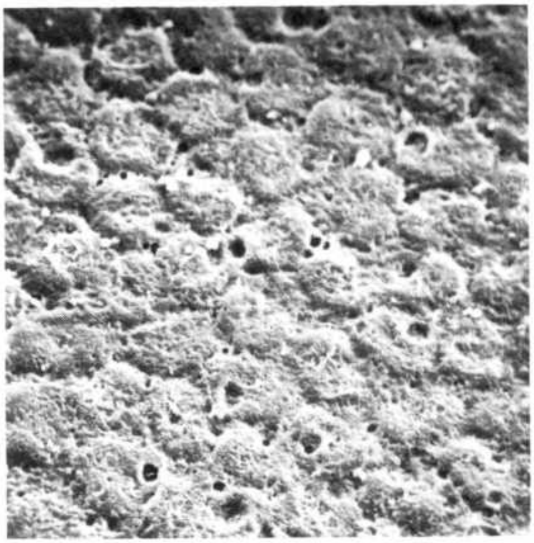

Fig. 2c

Fig. 2 *Scanning electron microscopy of the corneal endothelium.* (a) *Normal after 6 hours' perfusion in gluthathione bicarbonate Ringer (× 1150). All boundaries are well defined and the cell surface smooth.* (b) *Immediately after the freeze/thaw cycle (× 1050). Apparent prominent nuclei. Indistinct cell boundaries and a general surface pitting.* (c) *Six hours of perfusion after the freeze/thaw cycle (× 770). Rounded swollen cells with extensive surface pitting and fenestration.*

lack of water barrier function after freezing. This functional change was not a consequence of alterations in the swelling pressure of the corneal stroma, as similar thickening rates were achieved with both frozen and nonfrozen 'stromal' preparations. Toxicity studies at +4°C of the cryoprotective solutions showed that only minimal changes in both morphology and function occurred before freezing. The gross changes seen after thawing must therefore have been as a result of the freeze/thaw cycle.

In previous in-vitro studies histochemical staining was the primary technique of viability assessment. This method is an index of cell wall permeability to intracellular enzymes. Thus a cell that cannot retain enzymes is considered nonviable. The technique is a useful stage in the assessment of endothelial survival. However, although the staining technique indicated cell viability and whether there was complete cell cover, it gave little indication as to whether this was an integrated cell layer with water barrier and pump function. Specular microscopy and scanning electron microscopy gave more detailed information on the

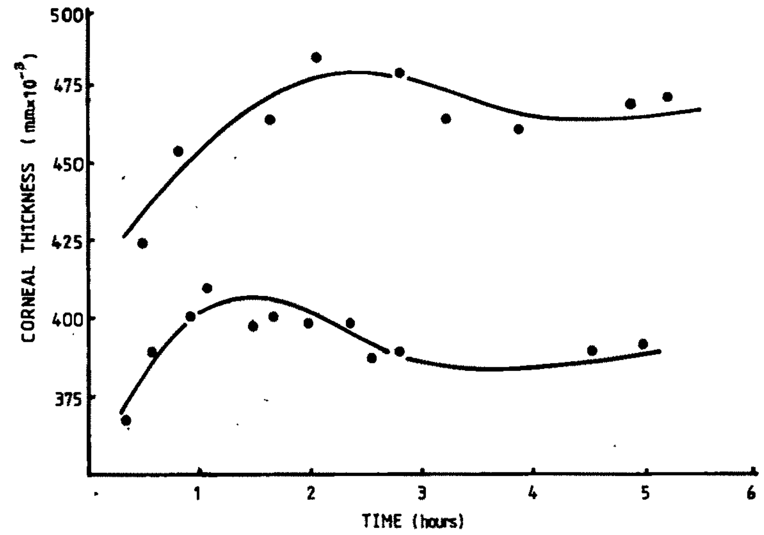

Fig. 3 *Functional assessment of nonfrozen cornea pretreated with cryoprotective solutions, with the specular microscope to measure corneal thickness.*

appearance of cell junctions and the cell layer. Both techniques showed that the cells were apparently all present immediately after the freeze/thaw cycle but had an atypical appearance. We consider that the bright areas seen with the specular microscope are cell nuclei. This image corresponds with the apparently elevated nuclei viewed by scanning electron microscopy. The techniques also gave evidence of individual cell breakdown during incubation, the dark areas shown by specular microscopy apparently correlating with individual cell rupture seen with the SEM. This disruption increases up to 6 hours, when SEM shows general disorganisation of the endothelial cell layer.

The lack of endothelial function after thawing was shown by the rapid increase in thickness. Such lack of water barrier function must be due to a combination of permeability changes in the endothelial cell wall, cell disruption, or loss of cell junction integrity, as pump inhibition alone would constitute a thickness increase of only 20 mm$\times10^{-3}$ h^{-1}. We and others[12] have shown that cell disruption and loss of integrity of cell junctions occur within hours. These changes could have been the manifestation of damage produced by freezing per se or have been caused by one of the many factors involved in post-thaw rehydration and the restarting of cell metabolism. The importance of the post-thaw period is further highlighted with in-

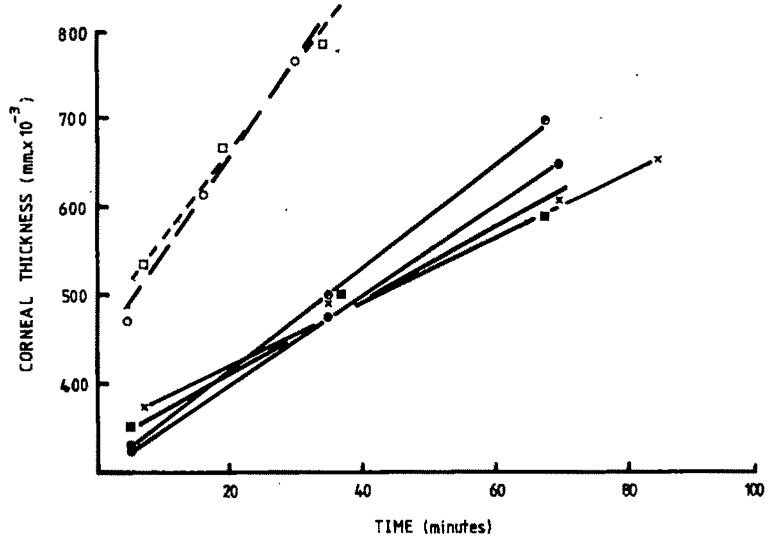

Fig. 4 *Functional assessment after the freeze/thaw cycle (solid lines). Thickness assessment of stromal preparations (interrupted lines):* □ *=frozen,* ○ *=non-frozen.*

vitro evidence of endothelial reversible damage.[11]

The aim of corneal cryopreservation is ultimate endothelial survival, not necessarily immediate normal function. Our results and other in-vitro studies[11 16] should be taken in the context of the clinical successes[17 18] that have been reported with cryopreserved corneae. It appears that there is a reorganisation of the endothelial layer after grafting. Postoperative corneae are opaque and nonfunctional, but clarity does return after several days.

There is therefore an indication for longer term studies, perhaps by employing organ culture as well as in-vivo techniques. Unfortunately the rabbit model is not suitable for long-term studies, as the endothelium is capable of rapid mitotic division.[19] The human situation of an adult nonreplicating endothelium must be studied directly, or with a different animal model system.

We therefore conclude that modern techniques of in-vitro assessment show that the endothelium has an atypical appearance and is nonfunctional immediately after corneal cryopreservation. However, in spite of this the good clinical results achieved in the past prove that there must be long-term endothelial survival. Nonetheless it should now be possible, with new methods of assessment, to improve systems of corneal cryopreservation. The further development of such techniques is currently in progress with this aim.

We are grateful to the Wellcome Trust Foundation and the South West Regional Health Authority for funding the project. We thank Professor Peacock and Dr M. O. Symes, of the Department of Surgery, Bristol Royal Infirmary, for their support. The use of the scanning electron microscopes of the departments of Physics and Zoology, Bristol University, is gratefully acknowledged.

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British Journal of Ophthalmology, 1982, **66**, 141–144

Eye injuries from car battery explosions

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SUMMARY Ten cases of serious eye injury from car battery explosions are reported. A survey of the instructions supplied with car batteries and battery chargers has been carried out. The mechanism and methods of prevention of such injuries are discussed.

Car battery explosions are an increasingly common cause of eye injuries.[1 2] This report draws attention to such injuries, and considers how their incidence and severity may be reduced by appropriate safety measures. We report 10 cases of serious injuries associated with car battery explosions. These are summarised in Table 1. Three cases are described in more detail.

Case reports

CASE 1

An 18-year-old engineer was measuring the charge of a car battery which had been on overnight trickle charge, when there was a spark and the battery exploded, injuring his left eye. On examination the corrected visual acuity was found to be 6/4 R and 6/24 L. There was an extensive acid burn of the left conjunctiva and cornea and a secondary uveitis. Intraocular pressure was 37 mm/Hg. The fundus was not clearly seen. He was treated with irrigation, topical steroids, and oral acetazolamide. Three days later the anterior segment had healed but the left visual acuity had deteriorated to 6/60. Examination revealed vitreous and retinal haemorrhage inferiorly and a full thickness macular hole (Fig. 1).

CASE 2

A 42-year-old company director was disconnecting the charger from a car battery which had been charging overnight when there was an explosion. His spectacles shattered, and he sustained a severe injury to his left eye. Visual acuity was 6/6 R and hand movements L. There were acid burns of both anterior segments and a penetrating injury of the left eye resulting in iris prolapse and traumatic cataract. After a successful primary repair and a later extracapsular cataract extraction he recovered 6/6 vision with a contact lens correction.

CASE 3

A 38-year-old car mechanic injured his right eye when a battery exploded while on charge. The cause of the explosion is unknown. His initial visual acuity was perception of light R and 6/9 L. There was a right corneoscleral penetrating injury with traumatic aphakia, and vitreous incarceration in the wound. A right relative afferent pupil defect and dense vitreous haemorrhage were also present. A primary repair was carried out, and the wound healed well. An ultrasound examination showed a dense vitreous haemorrhage

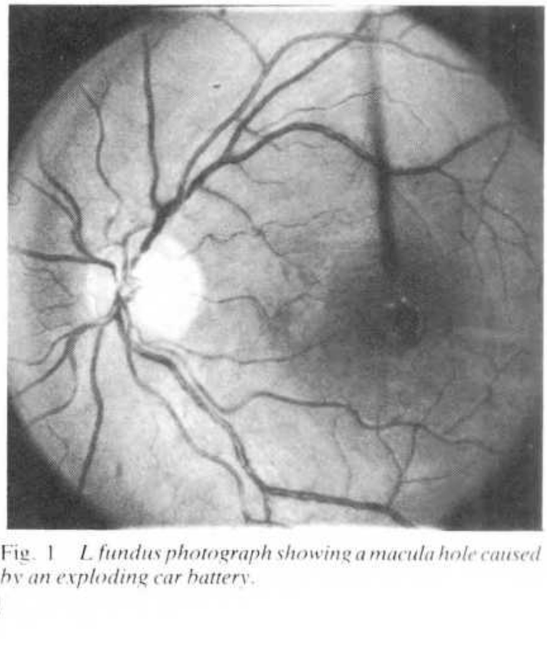

Fig. 1 *L fundus photograph showing a macula hole caused by an exploding car battery.*

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Table 1 *Details of cases*

Case No.	*Age*	*Sex*	*Occupation*	*Work/ home*	*Sequence of accident*	*Type of injury*	*Days in hospital*	*Final visual acuity*
1	18	M	Engineer	Work	Testing newly charged battery	Lid laceration; bilateral anterior segment acid burns; vitreous haemorrhage; macular hole	Nil	6/4R 6/60L
2	42	M	Company director	Home	Disconnecting charger leads from battery after overnight charge	Lid laceration; acid burns to both eyes; penetrating left eye injury; traumatic left cataract	25	6/6R 6/6L
3	38	M	Mechanic	Work	Battery exploded while on charge	Right penetrating injury; traumatic aphakia; vitreous haemorrhage; retinal detachment;	29	CFR 6/9L
4	40	M	Garage manager	Work	Testing newly charged battery when spark caused explosion shattering battery (See Fig. 2)	Facial lacerations; bilateral anterior segment acid burns	Nil	6/6R 6/9L
5	38	M	Farmer	Work	Tripped on charger lead to tractor battery, causing battery explosion	Bilateral anterior segment acid burns;	7	6/4R 6/4L
6	30	M	Driver	Home	Using jump leads	Bilateral anterior segment acid burns; left corneal laceration; left hyphema, vitreous haemorrhage, angle recession and secondary glaucoma	11	6/4R 6/4L
7	60	M	Actuary	Home	Disconnecting charger from battery after overnight charge	Bilateral anterior segment acid burns	7	6/6R 6/5L
8	70	M	Delivery driver	Work	Tripped on lead from battery charger to battery, causing explosion	Facial lacerations; bilateral anterior segment acid burns	2	6/9R 6/9L
9	39	M	Caretaker	Home	Newly charged car battery exploded	Bilateral anterior segment acid burns	5	6/5R 6/6L
10	25	M	Gamekeeper	Work	Recently charged industrial battery exploded. Right eye hit by fragment. Cause of accident unknown	Right optic nerve injury	10	HM R 6/9L

CF=counting fingers. HM=hand movements.

but a flat retina. Three weeks after the injury a right pars plana vitrectomy was performed. This revealed an inferior retinal detachment with subretinal blood and incarcerated retina. There was a small choroidal tear and yellow deposits around the disc thought to be myelinated nerve fibres or extruded myelin from an optic nerve injury. The macula appeared normal. 360° cryotherapy and an encircling procedure were carried out, and the retina subsequently reattached.

Sixteen weeks postoperatively the best corrected visual acuity was still only counting fingers. There was a dense right afferent pupil defect, clear media, a flat retina, and normal macula. It is likely that he had sustained an optic nerve injury or widespread photoreceptor damage at the time of the accident.

Discussion

There are 3 main mechanisms of injury from car battery explosions. Firstly, the acid released can give rise to chemical trauma; secondly, the concussive effect can cause injuries such as hyphaema, angle recession, and retinal oedema; and, thirdly, fragments of the battery or spectacles, if worn, can cause penetrating injuries. Fig. 2 shows the battery involved in case 4 and illustrates the number of fragments produced. The 10 cases show examples of all 3 mechanisms of injury (Table 2).

Nine of the patients sustained acid burns to the anterior segment of varying severity; 4 patients had severe contusion injury and 3 penetrating injuries. The patients who had acid injury or penetrating injury alone recovered normal vision. Two of the latter group, however, were rendered aphakic. Three patients had their vision reduced to 6/60 or worse in the injured eye as a result of the accident, and all were due to a contusional injury—to the optic nerve in 2 cases and the macula in one. The average inpatient stay was 9·6 days and the days lost from work would have been in excess of this. In none of the cases were any safety spectacles worn.

During the charging of a car battery hydrogen and

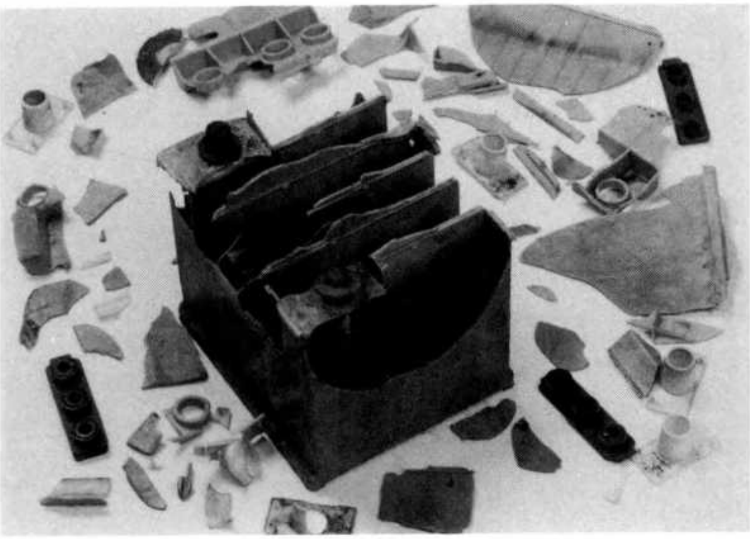

Fig. 2 *Exploded battery in case 4.*

oxygen are produced by electrolysis of water. Vent holes in the battery allow these gases to escape into the atmosphere. This venting system is thought to be very safe when the car is in normal use. When the battery is on charge, however, more gases are evolved and there is a greater risk of explosion, especially if safety precautions are not followed. There is no reliable information on the number of battery-related eye injuries, but it is known that the number of people doing their own car maintenance is increasing. A 1977 survey[3] estimated that 9·4 million households carried out their own car maintenance, and that there were at least 7·7 million home battery chargers in use, with 1 million new battery chargers purchased in the UK during 1977.

To assess whether adequate instructions and warnings of risks are supplied with batteries and chargers sold in this country we have carried out a small survey. We wrote to 7 manufacturers of battery chargers asking for the literature supplied with their products. Six of the 7 replied. The instructions gave varied advice. This is summarised in Table 3. A similar survey of 8 battery manufacturers produced 7 replies, summarised in Table 4.

Table 2 *Classification of injuries in 10 cases*

Type of injury	*Tissues injured*	*Number of cases*
Acid burn	Conjunctival and corneal burns	9
Contusion injury	Vitreous haemorrhage	3
	Optic nerve injury	2
	Angle recession, secondary glaucoma	1
	Macula hole	1
	Choroidal rupture	1
	Retinal detachment	1
Laceration or penetrating injury	Traumatic cataract	2
	Partial thickness corneal laceration	1
	Penetrating injury	2

Table 3 *Battery charger manufacturers: 6 replies from 7 sampled*

Safety point	*No. of manufacturers mentioning point*
1. Removal of battery from car before charging	1
2. Charge in well ventilated area	5
3. No naked flames	4
4. Correct mode of connection	6
5. Mains to be switched off before connecting or disconnecting	6
6. Warning of explosive risk	5
7. Protect eyes	0

Table 4 *Battery manufacturers (7 replies from 8 sampled)*

Safety point	*No. of manufacturers mentioning point*
1. Removal of battery from car before charging	5
2. Charge in well ventilated area	6
3. No naked flames	7
4. Correct mode of connection	7
5. Mains to be switched off before connecting or disconnecting	7
6. Warning of explosive risk	7
7. Protect eyes	3

All of the manufacturers who replied to our survey supplied lists of safety precautions to be followed with their products. Most accounts of safety precautions were adequate, but they were not always given prominence in the instruction leaflets. Only 3 manufacturers advised the protection of the eyes while charging batteries. Two failed to warn of the danger of using naked flame, and one manufacturer omitted any mention of the risk of explosion. Six of the 7 battery manufacturers fixed an acid-resistant label to the battery warning of the main risks and listing safety procedures. Since written instructions often become separated from the instrument, it would be helpful if this example could be followed by all battery and charger manufacturers.

Most eye injuries from car battery explosions are caused by neglect of safety procedures. Increasing public awareness of the risks by providing prominent warnings with batteries and chargers on sale would help to prevent such accidents. Furthermore, if people could be encouraged to wear eye protection, the severity of the injuries could be reduced.

We thank the consultants of the Oxford Eye Hospital, Mr D. McLeod and Mr. D. R. H. Lewis, for permission to report patients under their care, Mrs M. Herlihy and Mrs P. Lovelock for secretarial help, and the manufacturers who replied to the survey.

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British Journal of Ophthalmology, 1982, **66**, 145–148

Ocular injuries in Malawi

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SUMMARY A survey was made of 205 patients admitted to hospital for ocular trauma in Malawi in south-east Africa from January 1976 to December 1977. Results of the survey show that eye trauma is a relatively common problem in this developing country, occurring most frequently in children, young adults, and males. Most eye injuries in Malawi occurred under domestic circumstances; the major cause of ocular trauma was associated with chopping and gathering wood. Industrial injuries were rare. The most common injury was contusion and the most frequent complication was traumatic cataract. Most treated eyes retained useful vision.

Few general surveys of ocular trauma appear in the ophthalmic literature.[1–4] Most deal with penetrating injuries only,[5–9] childhood,[9–12] or adult[13] eye trauma, or injuries characteristic of a particular environment.[14,15] All of these surveys were carried out in developed industrial nations. Since many eye injuries are related to particular occupations and cultures, the types of injuries in developing countries are not necessarily similar.

Malawi, in south-east Africa, is a developing country with a population of about 5 million people, of which approximately 80% live in rural areas and engage in agriculture. Medical services in Malawi are free, including transportation to hospitals, but there is a considerable shortage of physicians, particularly specialists. Until the end of 1977 the central hospital in Blantyre was the only place in the country that had an ophthalmology department. All persons seeking treatment for severe ocular conditions were referred to this hospital for evaluation and treatment. We conducted a survey on eye injuries treated there during 1976 and 1977 and report the findings of our survey.

From January 1976 to December 1977 205 persons were admitted to Queen Elizabeth Hospital, Blantyre, for ocular injuries. Eight persons had bilateral injuries. Minor injuries such as conjunctival and corneal foreign bodies which could be treated on an outpatient basis were excluded from the study. All other cases were included and their records reviewed as for aetiology, time, type of injury, the treatment given, and its results.

Results and discussion

The average delay between occurrence of the injury and admission to the hospital was 10 days, with a range of 6 hours to 32 days. Many patients first resorted to folk medicine, reporting to the hospital only after such traditional methods failed and pain became intractable.

Patients ranged in age from 7 months to 68 years. Age and sex distribution are shown in Table 1. Table 2 compares the age distribution of patients in Malawi with that of patients in other surveys.

Table 1 *Age and sex distribution of patients treated for eye injuries*

Age	*No. of patients*	*Male*	*Female*	*Sex (ratio) M:F*
0–10	38 (18·5%)	27	11	2·5:1
11–20	33 (16·1%)	26	7	3·7:1
21–30	43 (21·0%)	32	11	2·9:1
31–40	34 (16·6%)	30	4	7·5:1
41–50	19 (9·3%)	14	5	2·8:1
Over 51	38 (18·5%)	29	9	3·2:1
Total	205 (100%)	158	47	3·4:1*

*Average.

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Table 2 *Geographical comparison of eye injuries by patients' ages*

	Age						*Sex ratio M:F*
	0–10	*11–20*	*21–30*	*31–40*	*41–50*	*Over 50*	
Malawi (1976–7)	38 (18·5%)	33 (16·1%)	43 (21·0%)	34 (16·6%)	19 (9·3%)	38 (18·5%)	3·4:1
Arkansas[2] (1937–54)	363 (21·1%)	306 (17·7%)	204 (11·9%)	178 (10·4%)	194 (11·4%)	469 (27·5%)	3·8:1
Iceland[3] (1965–76)	31 (29·5%)	24 (22·9%)	20 (19·9%)	12 (11·4%)	12 (11·4%)	6 (5·7%)	8·5:1
New Jersey[4]* (1969–72)	146 (31·2%)	86 (18·4%)	71 (15·2%)	90 (19·2%)†	—	75 (16·0%)	3·0:1

*Age groups reported as 0–9, 10–19, etc.
†Ages 31–50.

AETIOLOGY AND CAUSATIVE AGENTS

Analysis of the causes of trauma shows that more than half of the injuries were sustained at home or were associated with domestic pursuits (Table 3). 21% of the eye injuries were incurred in fights. Only 6·3% resulted from industrial accidents. As expected, few injuries were caused by traffic accidents, including bicycling accidents. A surprising finding is that only 1·5% of the injuries were related to agriculture, although 80% of Malawi's working population engage in agriculture. This finding may be attributable to the low level of farm mechanisation in Malawi and to the fact that eye injuries occurring in the fields often are not serious enough to warrant admission to hospital. In contrast, Ireland, a developed agricultural country, reported a high number of serious eye injuries incurred during agricultural pursuits.[15]

Reports from developed countries indicate that most injuries occurred during sports,[2] including children's play.[7] A 1923 survey from Scotland indicated that approximately 70% of the injuries were industrial in origin and that violence accounted for almost two-thirds of nonoccupational injuries.

Table 3 *Causes of eye injuries*

Cause of injury	*No. of cases*	*No. of males*	*No. of females*
Domestic			
Chopping wood	52 (25·4%)	39	13
Blunt instruments	17 (8·3%)	14	3
Sharp instruments	14 (6·8%)	11	3
Falls	7 (3·4%)	4	3
Burns (thermal)	2 (1·0%)	2	0
Other	23 (11·2%)	19	4
Total domestic	115 (56·1%)	89	26
Fights	43 (21·0%)	31	12
Industrial			
Blunt instruments	5 (2·4%)	5	0
Glass, earthenware	3 (1·5%)	3	0
Sharp instruments	1 (0·5%)	1	0
Burns (lye)	1 (0·5%)	1	0
Not recorded	3 (1·5%)	3	0
Total industrial	13 (6·3%)	13	0
Road accidents	12 (5·9%)	10	2
Agriculture	3 (1·5%)	2	1
Not recorded	19 (9·3%)	13	6

The most common single cause of ocular trauma in Malawi was wood chopping, undoubtedly because wood is almost the sole source of energy in its villages, and because of poor safety practices employed in chopping and gathering wood. Blows and falls, followed by injuries from sharp instruments, were the leading causes of eye injuries in other surveys.[1,2]

EYE INJURIES IN CHILDREN

As in other surveys children and young adults in our study constituted a sizeable proportion of patients with eye injuries. Nevertheless the percentage of eye injuries in persons under 20 was smaller in Malawi than in Arkansas (38·8%),[2] New Jersey (49·6%),[4] or Iceland (52·4%).[3] A possible explanation is the unavailability of potentially hazardous toys in Malawi as compared with developed nations. Indeed most eye injuries among children in Malawi occurred during domestic activities rather than play (Table 4), whereas games and sports accounted for most of the trauma for this age group in other surveys.

Table 4 *Causes of eye injuries in patients under 20 years of age*

Cause of injury	*No. of cases*
Chopping wood	18 (25·4%)
Blunt instruments	11 (15·5%)
Sharp instruments	7 (9·9%)
Fights	7 (9·9%)
Road accidents	3 (4·2%)
Industrial accidents	3 (4·2%)
Burns	2 (2·8%)
Falls	2 (2·8%)
Sports accidents	2 (2·8%)
Others	11 (15·5%)
Not recorded	4 (5·6%)
Total	71

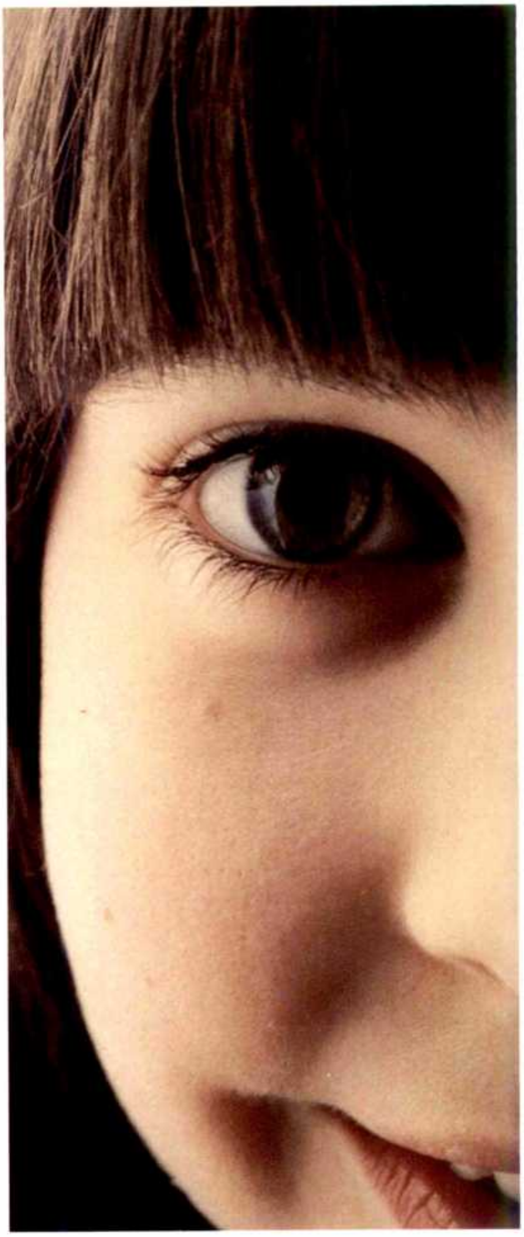

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Table 5 *Type of injury*

Type of injury	*No. of cases*
Contusion	85 (41·5%)
Penetrating injury	68 (33·2%)
Lid injury only	30 (14·6%)
Corneal erosion and foreign body	19 (9·3%)
Burns	3 (1·5%)

TYPES OF INJURIES

Contusions with severe intra- and extraocular complications constituted the greatest number of injuries in Malawi (Table 5). Two of the 3 burn cases were in epileptic children who fell into an open fire during a seizure. Contusions also comprised a high percentage of ocular trauma in industrial countries.[4] The relatively fewer penetrating injuries in developed countries were probably attributable to the better safety practices observed in those countries. The incidence of penetrating injuries in Malawi is similar to that reported in Scotland in the early 1900s.[1] Lack of education and inadequate safety practices may be common denominators.

OCULAR DIAGNOSIS

The main diagnoses made on the 205 patients are listed in Table 6. When more than one type of major lesion existed in one eye, both are listed. Eight patients had bilateral injuries: 4 of the 8 had blunt trauma resulting in cataracts in 2 instances and retinal oedema in 2; 4 patients had corneal erosions.

Table 6 *Diagnosis of ocular injuries*

Site of injury	*Total no. eyes*		*No. of injured eyes*
Cornea	65	Perforation with iris prolapse	39
		Severe erosion	17*
		Perforation without iris prolapse	9
Lens	65	Traumatic cataract	55
		Luxation, sublaxation	10
Anterior chamber	32	Hyphaema	32
Eyelids	32	Laceration	32†
Orbit	23	Haematoma	19
		Cellulitis	4
Sclera	25	Perforation	32‡
Vitreous	10	Haemorrhage	10
Conjunctiva	8	Severe haemorrhage	8
Retina	4	Haemorrhage and oedema	3
		Detachment	1
Iris	4	Iriodyalsis	4
Choroid	2	Choroidal tear	2§
Endophthalmitis on admission	11		
Secondary glaucoma	5		

*Eight with corneal foreign bodies.
†Two with canalicular involvement.
‡Twenty with corneal perforation.
§Without other ocular pathology.

Late arrival at the hospital and delayed treatment resulting from attempts at employing native medicine accounted for the 11 cases of endophthalmitis and 4 cases of orbital cellulitis in addition to primary trauma diagnosed on admission.

We saw no cases of retained intraocular foreign body and no orbital wall fractures, though we looked for these conditions in all patients who had relevant history and clinical findings. Scleral wounds in our series were more common than in others,[3 4–14] probably because in a less mechanised society eye injuries typically are caused by large, low-velocity objects rather than small, high-velocity objects that tend to produce corneal perforations and retained foreign bodies.

We saw only one case of retinal detachment, attesting to the fact that idiopathic retinal detachment is rare among blacks and that traumatic detachments are rarely seen.[16–17]

TREATMENT

Patients with nonpenetrating injuries of the eyeball were treated medically. Surgery was performed only to remove cataracts or for washout of nonresorbed hyphaemas. None of the 32 cases of hyphaema required enucleation of the eyes.

We performed surgery on patients with penetrating eye injuries on admission, repositioning the prolapsed iris as necessary, removing damaged lenses, and suturing lacerations. Vitrectomy, which in some instances might have improved the prognosis, could not be performed because of lack of appropriate instruments.

Other operations performed included repair of eyelids and canaliculi and removal of deep-seated corneal foreign bodies.

Twenty-seven eyes were blind and painful and considered to be beyond repair; 10 of the 27 were enucleated and 17 eviscerated. Eyes that were severely disorganised, with no chance of achieving any degree of visual acuity in patients, unlikely to return for follow-up examinations, were enucleated because of risk of sympathetic ophthalmia. One patient admitted for treatment of orbital haemorrhage died as a result of fracture of the base of the skull.

RESULTS OF TREATMENT

Best corrected visual acuity of the injured eyes, recorded from one to 6 months after admission, is shown in Table 7. The 101 patients with resulting visual acuity of 6/12 or better in the injured eye included those with eyelid and orbital injuries, superficial corneal and conjunctival injuries, and a few who

Table 7 *Visual acuity following treatment*

Visual acuity	*No. of eyes*
6/6–6/12	101 (47·6%)
6/15–6/20	17 (8·1%)
6/120–finger count	14 (6·6%)
Light perception only	18 (8·5%)
No light perception	31 (14·7%)
Not recorded	30 (14·2%)
Total	211

had corneal and scleral perforations, though most of the latter had a final visual acuity of less than 6/12. The patients with severe penetrating trauma and endophthalmitis, as expected, did rather poorly. Relatively poor results of treatment in this series are due, at least to a certain extent, to the late arrival of these patients for treatment.

Conclusion

Eye trauma occurs fairly frequently in developing countries and constitutes a major health problem. Efforts to prevent ocular injuries should particularly be directed toward improving established domestic habits, such as the methods of chopping and gathering wood. The necessity of seeking professional medical help immediately after injury and the danger of delaying treatment by first resorting to folk medicine should also be stressed. A campaign of this kind, however, is difficult to conduct in a country where schooling is not universal and much of the population has no access to mass media.

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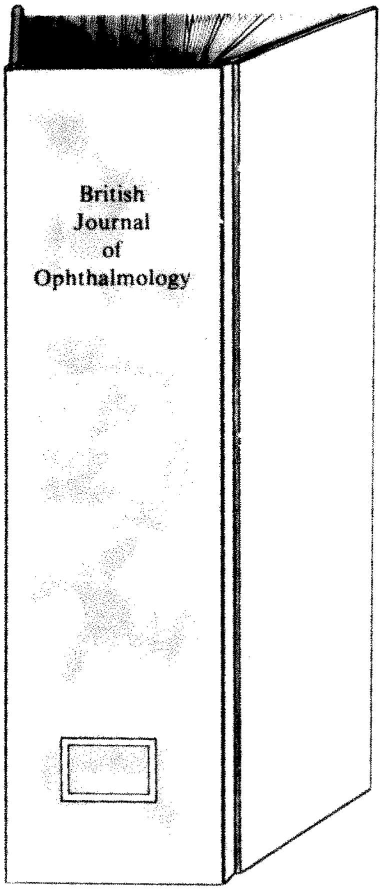

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ASTM CODEN BJOPAL 66 (2) 77-148 (1982) ISSN 0007-1161

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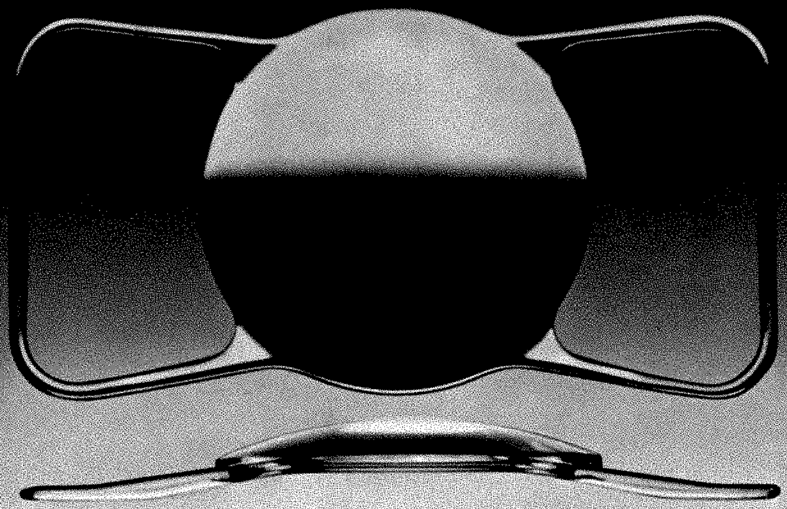

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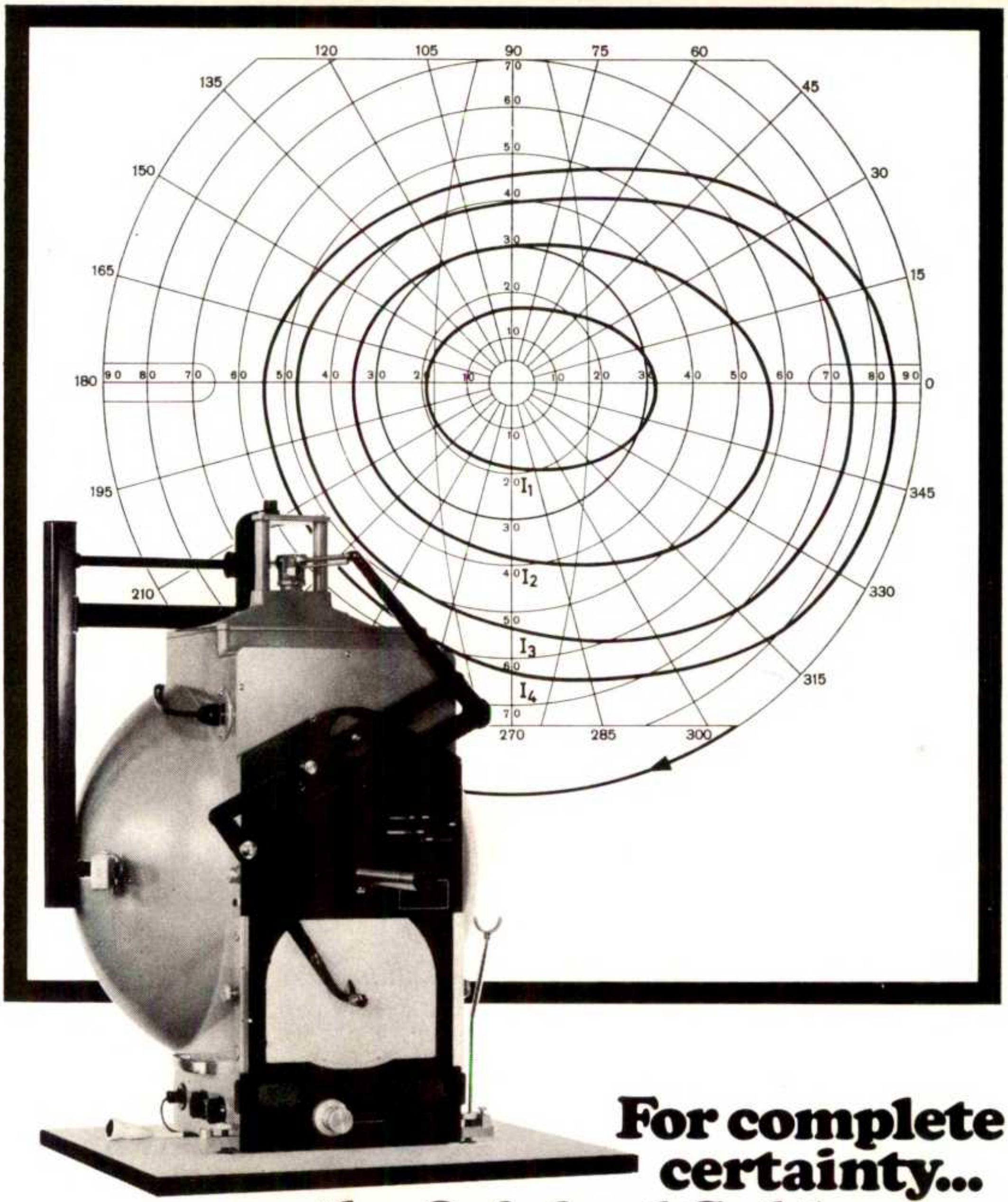

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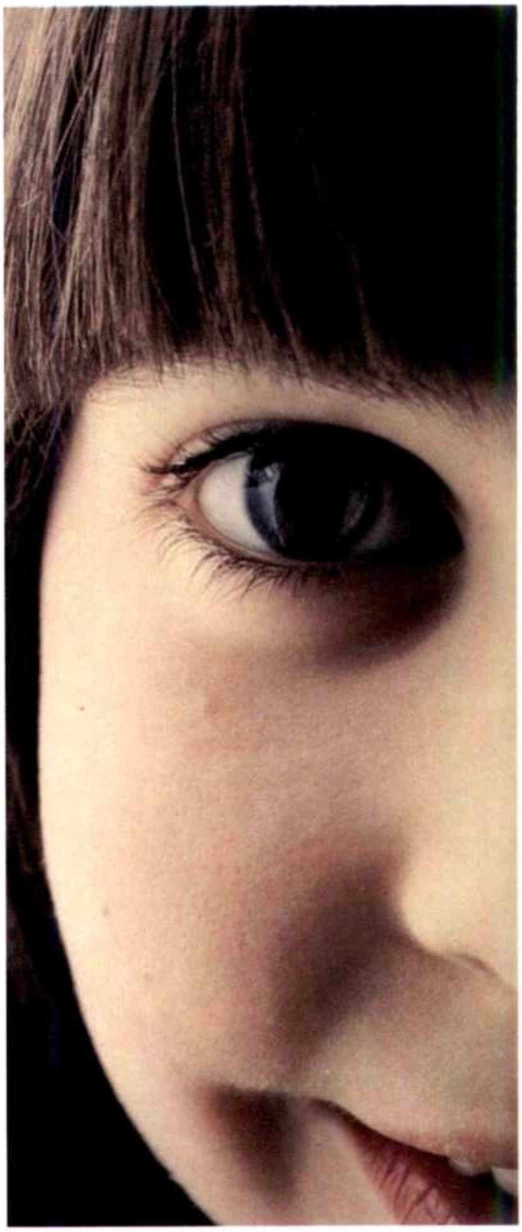

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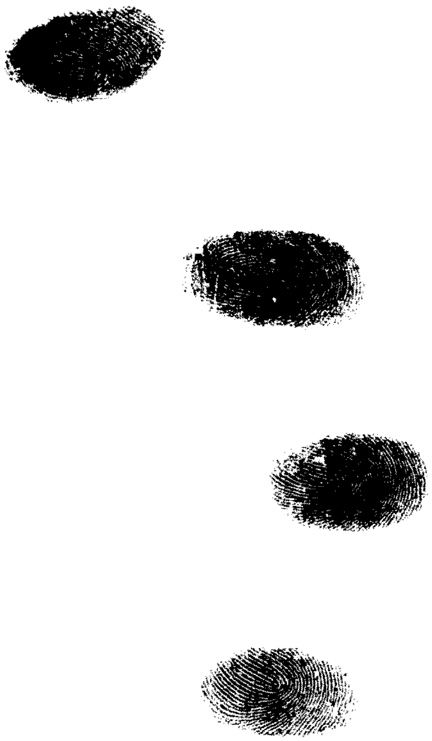

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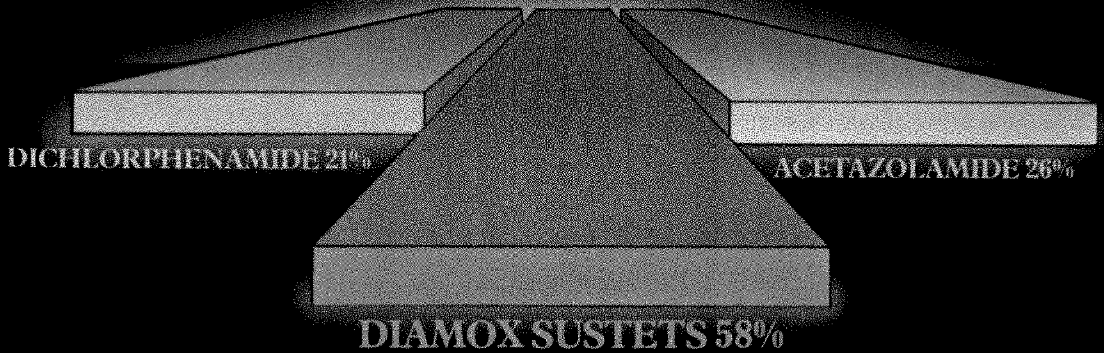

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British Journal of Ophthalmology, 1982, **66**, 149–154

Sickle cell retinopathy in young children in Jamaica

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SUMMARY Ophthalmological examinations were performed on 59 of the 74 (80%) children with homozygous sickle cell (SS) disease and on 37 of the 54 (69%) children with sickle cell-haemoglobin C (SC) disease, aged 5–7·5 years, within the cohort study of sickle cell disease. Arteriolar sheathing was the commonest retinal vessel abnormality, occurring in 30/59 (51%) SS children and in 11/37 (30%) SC children. Peripheral arteriolar closure was observed in 14 (24%) SS children and in 6 (16%) SC children. Arteriovenous anastomoses were seen in 3 children, but proliferative retinopathy was not identified. Capillary changes often occurred in patients without confluent closure, suggesting that complex remodelling of the capillary bed may precede retinal nonperfusion. Discrete retinal patches similar to schisis cavities resulting from intraretinal haemorrhages were found in 22 (37%) SS children and in 9 (24%) SC children, but haemorrhages were observed in only 2 patients (1 SS, 1 SC). Vitreous opacities were common and were generally associated with retinal vessel disease. Retinal changes were consistently more common in children with SS disease, though the differences failed to reach statistical significance. The prevalence of peripheral vascular closure and retinal patches showed a significant upward trend with age. These observations contrast with the greater prevalence of proliferative retinopathy characterising SC disease in adults.

Major visual loss in sickle cell disease may result from vitreous haemorrhage or retinal detachment, both consequences of proliferation of retinal blood vessels. It has been suggested[1,2] that peripheral arteriolar closure is the initiating event in an orderly progression of vascular changes culminating in the development of proliferative sickle retinopathy (PSR). PSR is more common in SC disease,[3-5] yet there is evidence that peripheral closure is equally common in homozygous sickle cell (SS) disease and sickle cell-haemoglobin C (SC) disease.[3,4] This implies that progression to PSR is not inevitable. Spontaneous resolution of PSR may occur more commonly in SS disease,[6] and the disparity between phenotypic expression of the 2 genetic abnormalities may reflect only a different predisposition to the development of preretinal blood vessels.

Retinal vascular changes in childhood have been reported rarely,[7] yet identifying early vascular abnormalities and their relationship to PSR may be crucial to the understanding of the genesis of PSR. A cohort study of sickle cell disease in which infants have been followed up from birth has provided an opportunity to assess the early retinal vascular changes in a well documented and representative sample of children with SS and SC disease.

Patients and methods

Since mid-1973 cord blood samples from approximately 95% of all nonoperative deliveries at the main Government maternity hospital (Victoria Jubilee Hospital) in Kingston, Jamaica, have been screened by electrophoresis on cellulose acetate and agar gel.[8] By 1 January 1981 a total of 89 020 infants had been screened, with the detection of 290 children with SS disease and 170 children with SC disease. These children, along with age/sex matched controls with a normal haemoglobin (AA) genotype, have been followed up in special clinics operated by the staff of the MRC Laboratories.

At the time of the present study (January 1981) all children with SS or SC disease aged over 5 years were invited to attend for ophthalmic examinations during a 3-week period. Of the available patients 59/74

Correspondence to Professor A. C. Bird.

(80%) children with SS disease and 37/54 (69%) children with SC disease attended. Ten normal control children representing all normal controls with appointments during the 3-week study period were also examined. The average age of each group was 6 years 3 months (range 5–7·5 years).

Visual acuity was measured by Snellen's test type or the illiterate E test at 6 metres. Fundus examination was performed by direct and indirect ophthalmoscopy with the pupils dilated. Fluoroscopy and angiography were carried out in patients with identifiable disease and routinely in those over 6·5 years, amounting to 35 children.

Results

VISUAL ACUITY

In 8 patients it was impossible to obtain an accurate assessment, but in the remaining 88 children acuity was 6/9 or better.

RETINAL VASCULATURE

Arteriolar sheathing, as distinct from the altered vascular reflex occurring in diffuse peripheral disease, was recorded in 30/59 (51%) SS children and in 11/37 (30%) SC children. Opacification of the vessel wall was generally confined to either side of the blood column over long segments, but total opacification was seen in 2 patients in both of whom vessel patency was confirmed by fluoroscopy.

Peripheral closure, diagnosed on the basis of fluorescein angiography or fluoroscopy, was observed in 14/59 (24%) SS children and in 6/37 (16%) SC children (Fig. 1). The extent of closure varied between 60° and 360° of the circumference at the periphery and always affected the temporal side.

Circumferential arteriovenous anastomoses (Fig. 1) were visible ophthalmoscopically in 3 patients, all with closure. An elevated vascular loop which leaked fluorescein was observed at the edge of an area of closure in 2 children with SS disease.

Coarsening of the capillary bed (Figs. 2, 3) was observed posterior to areas of closure but also occurred in some patients without closure. Other microvascular changes included aneurysmal dilatation of vessels (Fig. 3), arteriolar bypass channels, arteriovenous communications, and abnormal tortuosity (Fig. 4).

Pathological avascular zones in the macular region were not seen.

HAEMORRHAGE

Single peripheral intravitreal haemorrhage occurred in 2 patients (1 SS, 1 SC). The preretinal blood was not obviously associated with intraretinal haemorrhage or forward vessels, though in both cases the haemorrhage occurred at the junction of perfused and occluded capillary beds. One of these patients had an additional linear intraretinal haemorrhage.

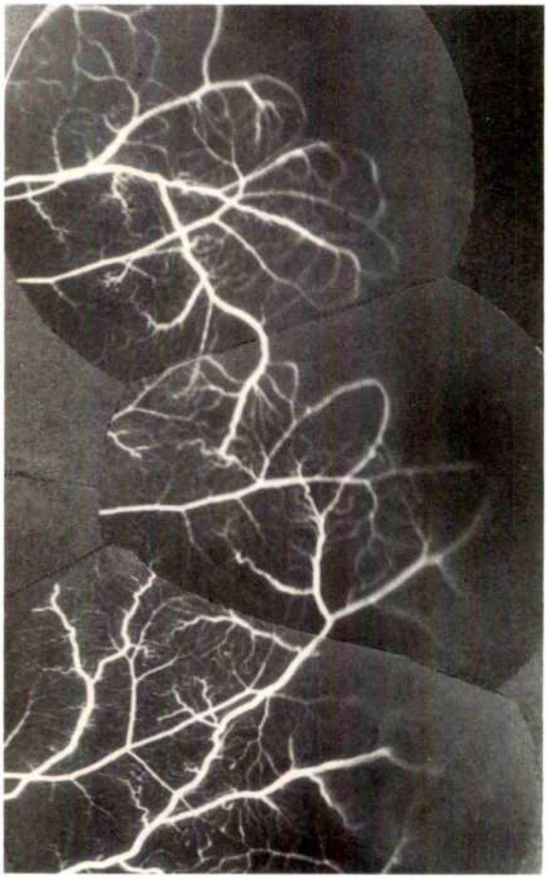

Fig. 1 *Fluorescein angiography demonstrating peripheral retinal nonperfusion and arteriovenous anastomoses in a male with HbSS aged 7 years.*

PERIPHERAL RETINAL CHANGES

Discrete retinal patches of discoloration occurred in 22 (37%) SS children and in 9 (24%) SC children. These lesions varied from 0·5 to 3 mm in diameter, and there were up to 12 lesions in any eye. Some were flat, varying in colour from brown to grey, and were occasionally associated with irridescent spots within them. Others were raised and were frequently a similar colour to, or darker than, the adjacent retina and were surrounded by a light reflex. One lesion appeared to be cystic. Some patches had a central white spot which itself was occasionally raised. There was no evidence of a recent haemorrhage associated with a patch.

Fluorescein angiography of these lesions was

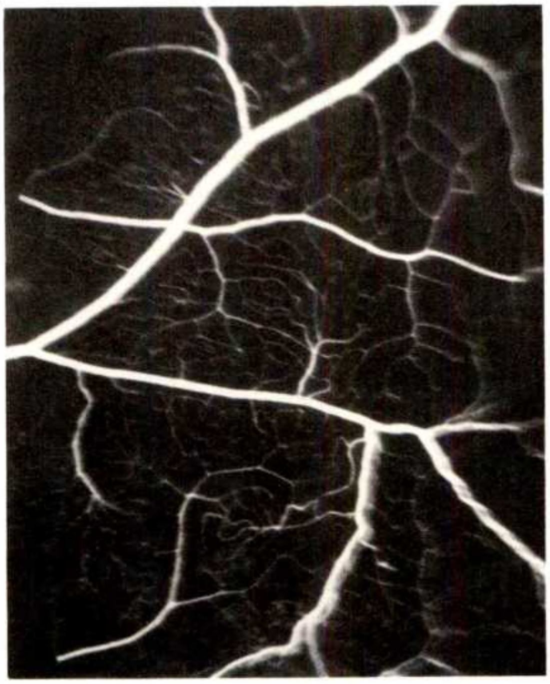

Fig. 2 *Fluorescein angiography of the peripheral retina showing coarsening of the capillary bed in a female with HbSS aged 6 years 6 months.*

usually normal, although some showed transmission defects at the level of the retinal pigment epithelium. There was no masking by the lesions, and the overlying capillary bed was unaltered.

A diffuse retinal colour change, observed in 27 (46%) SS children and in 10 (27%) SC children, consisted of a poorly defined irregular variation in the colour of the peripheral retina, varying between yellow and red, extending in some cases behind the equator but always to the ora serrata. This change was noted predominantly in the inferior retina. Fluorescein angiography showed that masking, leakage, and peripheral closure were not necessarily associated with an area of colour change, though some had transmission defects. Where there was closure in an area of colour change, it could be defined only by angiography.

Only one patient had peripheral retinal whitening, which occurred in one quadrant. This was not associated with closure, masking, or leakage on angiography.

Proliferative retinopathy was not seen in either group in this study.

VITREOUS CHANGES

Greyish condensation of the vitreous base (vitreous veils) was found in 18 (31%) SS patients and in 8 (22%) SC patients. This appeared as radial multilayered opacities in the peripheral vitreous, and was associated with retinal abnormality in every case except one patient with SC disease, though fluoroscopy was not performed in this case.

RELATIONSHIP BETWEEN AGE AND GENOTYPE (Table 1)

Retinal and vitreous changes were observed in all age groups but only peripheral vascular closure ($p<0\cdot05$) and retinal patches ($p<0\cdot01$) showed a significant upward trend with age (by the Mantel-Haenszel χ^2 test for trend with age, allowing for genotype). Closure was seen in a patient as young as 5 years 4 months. Sheathing, peripheral colour change, and vitreous veils failed to show any significant age relationship. All the abnormal findings were more common in SS than in SC disease, but by a similar χ^2 test for difference between genotypes and allowing for age they failed to show significant differences.

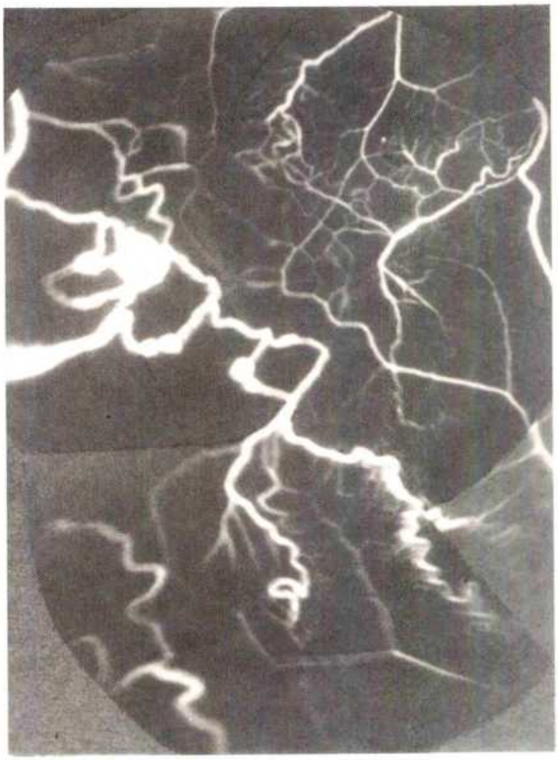

Fig. 3 *Fluorescein angiography of peripheral retina showing coarsening of the capillary bed, areas of retinal nonperfusion, and aneurysmal dilatation of retinal vessels in a male with HbSS aged 6 years 11 months.*

Table 1 *Vitreous and retinal changes correlated with age*

Age (months)	*Genotype*	*Number*	*Sheathing*		*Closure*		*Peripheral colour change*		*Patches*		*Vitreous opacity*	
60–71	SS	23	11	48%	3	13%	10	43%	7	30%	6	26%
	SC	10	2	20%	0		5	50%	1	10%	3	30%
72–83	SS	22	10	45%	5	23%	9	41%	5	23%	7	32%
	SC	20	6	30%	4	20%	3	15%	5	25%	3	15%
84–90	SS	14	9	64%	6	43%	8	57%	10	71%	5	36%
	SC	7	3	43%	2	29%	2	29%	3	43%	2	29%
Total	SS	59	30	51%	14	24%	27	46%	22	37%	18	31%
	SC	37	11	30%	6	16%	10	27%	9	24%	8	22%
	Both	96	41	43%	20	21%	37	39%	31	32%	26	27%

INTERRELATIONSHIPS BETWEEN RETINAL FINDINGS

When the association between each pair of variables was examined in all age groups and genotypes combined, highly significant relationships were apparent between closure and sheathing (p<0·001) and closure and retinal patches (p<0·001), and between sheathing and peripheral colour change (p<0·001) and sheathing and patches (p<0·01). No significant relationships were apparent between peripheral colour change and closure or between peripheral colour change and patches. Of the 20 patients with closure 17 had sheathing and 14 had patches; all patients with closure demonstrated either sheathing or retinal patches (Table 2).

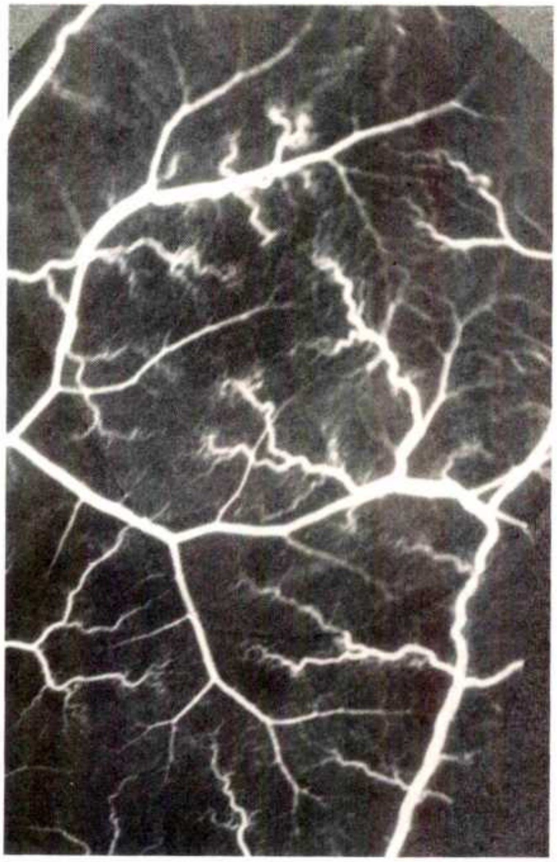

Fig. 4 *Fluorescein angiography of peripheral retina showing tortuosity of retinal vessels and an abnormal pattern of arterioles and venules in a female with HbSS aged 7 years 5 months.*

FINDING IN CONTROLS

The retina, retinal vessels, and vitreous were entirely normal in 9 controls, but layered radial opacities in the vitreous were observed in one control.

Discussion

RETINAL VESSEL CHANGES

This study indicates that retinal vascular disease occurs in both SS and SC disease before the age of 6 years. Peripheral nonperfusion was more common with advancing age, but it is possible that reluctance to perform fluoroscopy on all patients may have led to an underestimate of its prevalence. Although proliferative retinopathy was not seen, arteriovenous anastomoses were apparent in 3 patients; the close temporal relationship between arteriovenous anastomoses and PSR observed in older populations

Table 2 *Relationship between arteriolar closure and other retinal findings*

	Patients examined (96)			
	Closure		*No closure*	
Total	20		76	
Sheathing alone	6	30%	15	20%
Retinal patches alone	3	15%	8	11%
Sheathing and patches	11	55%	9	12%
No sheathing or patches	0		44	58%

(unpublished observations) implies that PSR may soon develop in this patient group.

Opacification of the arteriolar walls was relatively common in children with SS and SC disease but did not occur in control children. In most cases this was apparent only at the edge of the blood column, but in 2 patients the whole blood vessel wall was opaque. The sheathing affecting long segments of the retinal blood vessels simulated sheathing seen in retinal ischaemia rather than the multifocal opacifications seen in retinal vasculitis or following embolism without prolonged ischaemia. However, it is difficult to accept that there had been prolonged retinal ischaemia in the presence of an intact capillary bed, though it is possible that transient ischaemia causes greater endothelial damage in sickle cell disease than in patients with a normal genotype. That vascular obstruction had occurred is supported by the presence of arteriolar by-pass channels seen in one patient without arteriolar occlusion.

In 1971 Goldberg[1] suggested that retinal arteriolar occlusion was the initiating event in sickle cell retinopathy, but his study on peripheral remodelling[9] and observations on these children imply a more complex sequence of events. If sheathing is evidence of primary vascular disease, it predates capillary changes in many patients. Coarsening of the capillary beds with large, long capillaries which were fewer than normal occurred without closure in some children and appeared to predate retinal nonperfusion. These observations imply that closure occurs after complex capillary remodelling, which may be a response to intermittent or chronic vascular compromise occurring over a period of time. This is not to deny that the obstruction is at the arteriolar level but to suggest a more complex process than solitary arteriolar obstruction.

NEURORETINAL CHANGES

Discrete retinal patches of a red or brown colour occasionally containing glistening reflexes were one of the commonest findings, occurring in 31 patients, and were frequently multiple in an affected eye. These lesions had some characteristics previously ascribed to 'schisis cavities,' which are thought to arise from the resolution of intraretinal haemorrhages.[10,11] If the same mechanism applies to these lesions in children, it implies that previous intraretinal haemorrhage must have been common in this group. During the study period an intraretinal haemorrhage was identified in only one patient and another patient had a localised haemorrhage in front of the retina which might have resulted from an intraretinal haemorrhage rupturing through the inner limiting membrane. The presence of a normal capillary bed in many of the patches suggests that the process which gives rise to haemorrhage, and the haemorrhage itself, do not necessarily have any discernible affect on the retinal vasculature.

Peripheral retinal colour changes did not occur in controls and were presumably related to sickle cell disease. The colour changes were not due to retinal pigment epithelial abnormalities as fluorescein angiography showed no alteration of pigment epithelial transmission characteristics. Condon and Serjeant[3,4] attributed whitening of the peripheral retina to oedema which resolved as the neuroretina became thinner, but fluorescein angiography showed no evidence of retinal oedema in the present study. Intermittent vascular obstruction might cause multifocal and ill-defined areas of retinal thinning due to infarction, with consequent changes of the vitreous base and inner limiting membrane. This would be homologous to the facets seen in the posterior retina.[12] Such a hypothesis could be tested only by histopathological examination of the affected eyes.

VITREOUS CHANGES

Layered radial opacities in the vitreous base were common in children with SS and SC disease but also occurred in one control. Retinal vascular disease would be expected to influence the vitreous, and vitreous detachment occurs early in patients with sickle retinal vascular disease. All but one of the patients with vitreous veils had signs of retinal vascular disease.

Few controls were examined, so that identification of abnormalities was based partly on comparison with known fundus appearances. However, striking retinal changes were frequent in the study group, and it is apparent that retinal vascular disease is well established in children between 5 and 7·5 years. Although qualitatively similar in SS and SC disease, most retinal vessel abnormalities were more common in SS disease in contrast with a higher prevalence of PSR observed in SC disease during adult life. Apart from the eye, vascular disease is accepted to be more common in SS disease, and our evidence implies that this also applies to vessels in the peripheral retina. If this is confirmed, then the high prevalence of PSR in SC disease must be related to factors other than simple vessel occlusion.

We are grateful to Mr Patrick Condon for valuable discussion. This work was supported in part by grant PHS 15168 from the National Heart Lung and Blood Institute.

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British Journal of Ophthalmology, 1982, **66**, 155–160

Macular vasculature, visual acuity, and irreversibly sickled cells in homozygous sickle cell disease

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SUMMARY Observations of visual acuity and the conjunctival, macular, and perimacular vascularity have been assessed in patients with homozygous sickle cell (SS) disease. There were 17 matched pairs, each consisting of one patient with a high count ($\geq 15\%$) and one with a low count ($\leq 5\%$) of irreversibly sickled cells (ISCs). The macular vascular bed was assessed by measurements of the foveal avascular zone (FAZ), perimacular avascular zones, and counts of perimacular vascular abnormalities (perimacular counts). Small foveal avascular zones and high perimacular counts were commoner in younger than older patients and there was a significant inverse correlation between size of the FAZ and the perimacular count. These observations were compatible with the hypothesis that perimacular vessel anomalies represent the early vaso-occlusive phase which progresses to ischaemia and the formation and enlargement of avascular areas. Visual acuity was assessed by Snellen's test type and by measuring contrast sensitivity. There was no obvious relationship between acuity measured by the 2 methods and no relationship between acuity and observations of macular vascularity. High ISC counts were significantly related to abnormalities of the conjunctival vasculature, but no relationship was noted with abnormalities of the macular vasculature or with visual acuity.

The small-vessel obstruction characteristic of sickle cell disease may affect the retinal vasculature. Although peripheral retinal vessel involvement is most widely documented, capillary drop-out and vascular remodelling at the posterior pole has also been reported[1 2] and may be associated with a reduction of visual acuity. Such macular capillary occlusion is assumed to be secondary to intravascular sickling and thus might be related to the irreversibly sickled cell (ISC) count, as in the relationship previously shown with the degree of vessel obstruction in the conjunctival vasculature.[3]

This hypothesis has been tested in the present study by examining the visual acuity and macular capillary vasculature in matched groups of patients with homozygous sickle cell (SS) disease with high ($\geq 15\%$) and with low ($\leq 5\%$) counts of irreversibly sickled cells.

Materials and methods

Patients were selected from among adults attending the sickle cell clinic of the University Hospital of the West Indies. Twenty patients (10 male, 10 female) with SS disease and with steady-state ISC counts of 15% or above were selected at random from clinic files and matched by age and sex with 20 patients in whom ISC counts were 5% or below. The ISC count is thought to reflect the degree of intravascular sickling, which may vary markedly between different patients with SS disease. Measured by a differential red cell count, ISC counts may vary from 0–40% in different patients, but within individual patients the counts oscillate within a relatively narrow range characteristic of the individual patient.

All patients were given appointments for ophthalmological examination during the 3-week period of the study, but of these only 8 pairs of male patients and 9 pairs of female patients actually attended. Ages ranged from 20 to 49 years with a mean age of 30

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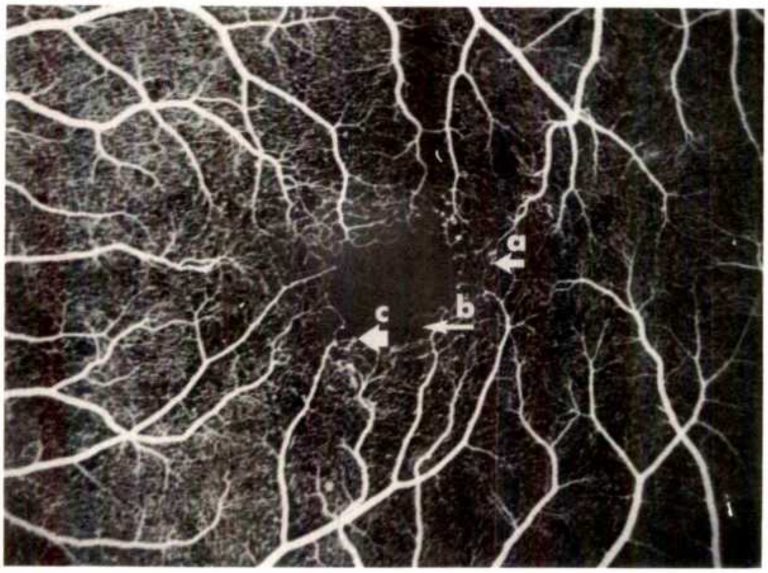

Fig. 1 *Fluorescein angiogram of perimacular region in a 23-year-old female patient demonstrating enlarged FAZ, microaneurysm* (a), *perimacular avascular zone* (b), *and hairpin loop* (c).

years. The diagnosis of SS disease was based on the finding of a single major haemoglobin band in the position of HbS on haemoglobin electrophoresis on cellulose acetate and agar gel, compatible HbA_2 levels, and family study where possible.

Visual acuity was assessed as best corrected vision with Snellen's test type. Contrast sensitivity was assessed with plates 2–7 of the Arden gratings,[4] greater contrast being gradually exposed successively until the grating was detected by the patient. The reading was scored at this point and the scores of all 6 plates added to give a total score for each eye. The conjunctival vasculature was assessed in all quadrants of each eye with the use of a photoslit lamp, and the vessel anomalies were graded according to the classification of Serjeant *et al.*[3] The optic discs and maculae of both eyes were photographed in colour with a Zeiss retinal camera and ×2 lens, and the films were examined for abnormal vessels. Angiography of the macular areas of both eyes was performed and the angiograms examined on a Zeiss Dokumator with a ×17·5 lens to determine the foveal and perimacular avascular zones and the number of perimacular capillary abnormalities. The foveal avascular zone was measured as the mean of vertical and horizontal diameters and expressed as an average for both eyes. Perimacular avascular zones (Fig. 1) were assessed in an arbitrary circle of 2·4 mm diameter centred on the macula. They were arbitrarily graded into scores 0–3 varying from no detectable capillary drop-out to moderate capillary drop-out, and the scores for each pair of eyes were added to give a total score for each patient. Perimacular capillary abnormalities (perimacular counts) were assessed within the same 2·4 mm circle by counting the number of microaneurysms, dilated capillaries, dark and enlarged arteriolar segments, and hairpin-shaped vascular loops (Fig. 1, 2). The total count of abnormalities in each pair of eyes was then calculated.

All assessments were performed by one ophthalmologist (R.J.M.) without knowledge of the ISC count.

Results

VISUAL ACUITY

Visual acuity measured by Snellen's test type was 6/6 in 50/68 (74%) eyes and 6/12 or better in 65/68 (96%) eyes. Acuity was 6/24 in one eye affected by vitreous haemorrhage and 6/36 in 2 eyes with long-standing aphakia. There was a tendency for reduced acuity to be more common in older than younger patients, acuity of less than 6/6 occurring in 4/20 patients under 30 years compared with 8/14 patients over this age. This difference just failed to reach statistical significance ($p=0·06$).

The Arden grating scores showed considerable variation, though there was generally good agreement between results in both eyes of the same patient. Scores varied between 57 and 114 in individual eyes (mean score 85), and pathological scores as defined by Arden and Jacobson[5] in British populations (>82) occurred in 37/67 (55%) of eyes in this patient group. There was a tendency for scores to be higher in female patients (mean±SD: 89·4±12·4) than male

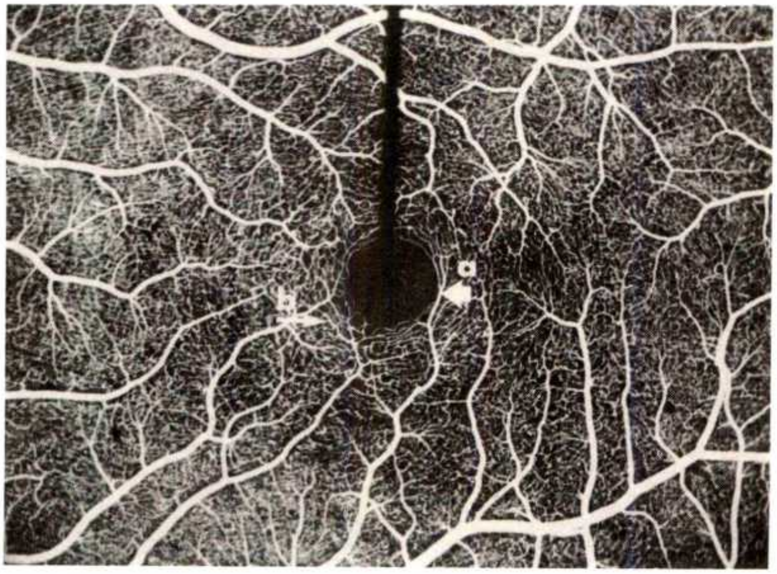

Fig. 2 *Fluorescein angiogram of perimacular region in a 20-year-old female patient demonstrating a normal FAZ but with an enlarged arteriole forming part of the perifoveolar arcade* (a), *and a dilated arteriolar segment* (b).

(79·0±13·9), the difference being statistically significant ($p<0·05$), but there was no significant relationship with age.

There was no obvious relationship between scores with the Arden gratings and with Snellen's test type (Fig. 3) and no relationship between acuity measured by either method and the ISC count.

CONJUNCTIVAL VESSEL ABNORMALITIES

There was good agreement between the scores in the quadrants of both eyes, and a total score (obtained by adding scores in all 8 quadrants) was therefore used in the statistical analysis. The previously reported positive relationship between ISC count and conjunctival vessel abnormalities was confirmed (Table 1), and an effect of age was also noted. In younger patients, who had a wide spread of scores, higher scores were associated with high ISC counts, whereas most of the older patients had high conjunctival scores regardless of their ISC count (Fig. 4). How-

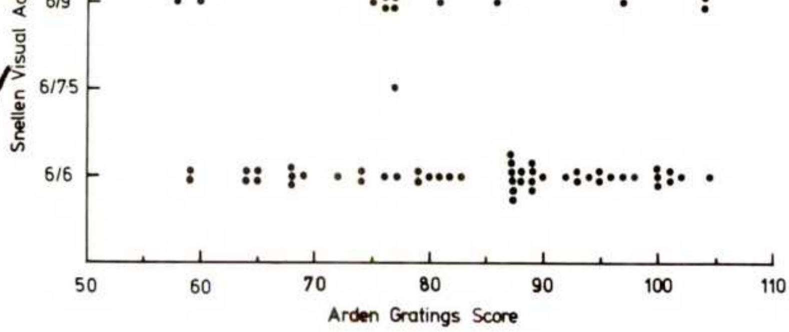

Fig. 3 *Comparison of visual acuity measured by Snellen's test type with contrast sensitivity assessed by Arden's gratings. Each point represents one eye* ($n=67$)*; one eye with visual acuity of 6/24 was not assessed by Arden's gratings.*

Table 1 *Comparison of contrast sensitivity, conjunctival score, and macular abnormalities in patients with high and low ISC counts*

	Mean of high ISC group	*Mean of low ISC group*	*Paired t statistic*	*Significance*
Arden gratings	83·4	86·0	−0·91	NS
Conjunctival score	18·9	12·9	2·56	$p<0·05$
Foveal avascular zone (mm)	0·66	0·71	−1·23	NS
Perimacular avascular zones	1·1	1·9	−1·89	NS
Perimacular count of abnormalities	212	173	1·31	NS

See text for explanation of variables. NS=not significant.

ever, sample sizes within age groups were too small for the latter observation to be statistically significant.

MACULAR FINDINGS

Accurate observations on the macular vasculature were not possible in 10 eyes because of medial opacities in 4 and poor angiographic quality in 6. In cases where both maculae were visible there was generally good agreement between the eyes in respect of the foveal avascular zone and perimacular avascular zones, and though there was considerable variation in perimacular counts between the 2 eyes this variation was considerably less than the variation between patients. In cases where macular observations were unavailable in one eye observations on the other eye were used as best estimates of the missing observations.

The diameter of the foveal avascular zone varied from 0·46 to 1·03 mm and was positively correlated with the grading of perimacular avascular zones ($r=0·50$; $p<0·01$). Perimacular counts varied widely (total counts varied from 58 to 398) and showed a significant negative relationship with the foveal avascular zone ($r=-0·46$; $p<0·01$) (Fig. 5).

Foveal and perimacular avascular zones tended to be larger in the low ISC group and perimacular counts to be higher in the high ISC group, but none of these relationships were statistically significant (Table 1). High perimacular counts were confined to young patients, counts in excess of 225 occurring in 10/21 patients ≤30 years compared with 0/12 patients over this age ($p<0·01$; Fisher's exact test). Small foveal avascular zones were also more common in young patients, a mean diameter of <0·65 mm occurring in 9/21 patients ≤30 years compared with 1/12 patients over this age, but the difference was not significant.

None of the above macular findings showed significant relationships with conjunctival vessel abnormalities or with visual acuity assessed by either Snellen's test type or the Arden gratings.

OPTIC DISC

Saccular dilatations of small vessels on the optic disc occurred in 11/17 (65%) patients in the high ISC group compared with 7/17 (41%) patients in the low ISC group ($\chi^2=1·06$; not significant).

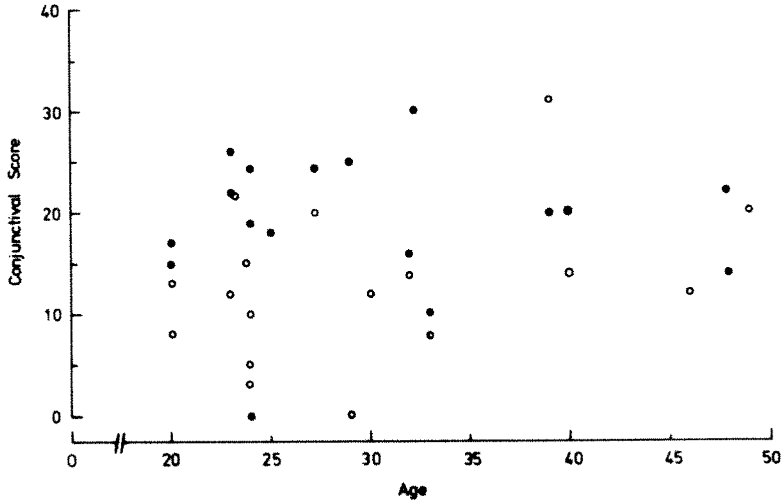

Fig. 4 *The relationship of total conjunctival score and age in patients with high (●) and low (○) ISC counts.*

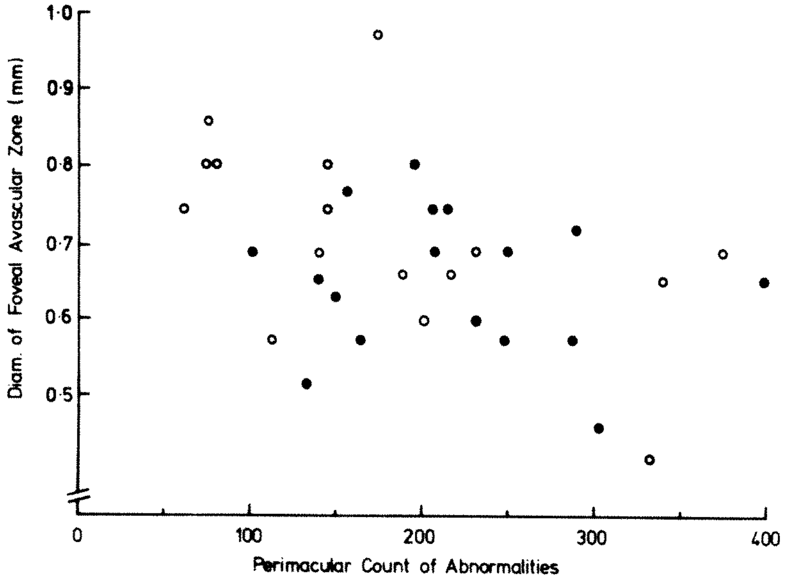

Fig. 5 *The relationship of foveal avascular zone (mean of both eyes) and perimacular count (total in both eyes) in patients with high (●) and low (○) ISC counts.*

Discussion

The previously reported association between the number of irreversibly sickled cells (ISC count) and the density of abnormalities in the conjunctival vasculature has been confirmed in the present study. An additional observation has been that this relationship was most apparent in young patients, those over 35 years of age tending to have frequent conjunctival vessel abnormalities regardless of their ISC count, though sample sizes were small and this finding was not statistically significant. If confirmed in larger groups of patients this observation would be difficult to explain unless repeated but transient vessel obstructions and endothelial damage result in cumulative and permanent vascular damage in the conjunctival vasculature. This hypothesis could be tested by serial observations on the conjunctival vasculature of older patients to confirm whether the pattern of conjunctival vessel anomalies is permanent, and not transient and constantly changing as in younger patients.

In contrast to observations in the conjunctival vasculature no relationship was apparent between the ISC count and abnormal vessels either in the macular area or on the optic disc. Saccular dilatations on the optic disc and perimacular abnormalities were both more common in the high ISC group, but the differences failed to reach statistical significance. There was no evidence that a high ISC count contributed to larger avascular zones at the fovea or in the perimacular area, and although the difference failed to reach significance there was a tendency for the larger avascular zones to occur in the low ISC group. The negative relationship between perimacular vascular abnormalities and the diameter of the foveal avascular zone is explicable if these features represent different stages of the same pathological process. An early vaso-occlusive phase manifested by multiple small-vessel anomalies may progress to total ischaemia and areas previously containing anomalies become replaced by perimacular avascular zones or enlargement of the foveal avascular zone. This is supported by the preponderance of small foveal avascular zones and of high perimacular counts in young patients and also by the elegant serial observations on macular and perimacular vascular remodelling of Asdourian and coworkers.[2]

The failure of the ISC count to correlate with any of the macular abnormalities presumed to result from vaso-occlusion casts doubt on the adequacy of this index in reflecting intravascular sickling in the retinal circulation. This observation conflicts with the association between high ISC counts and vessel anomalies in the conjunctival vasculature, but the latter circulation clearly represents an unusual and specialised capillary bed. It is a predominantly 2-dimensional surface circulation exposed to temperature variability and high oxygen tensions atypical of other circulations. It is possible that under these conditions sickled cells which are capable of reverting to the normal discoid shape do so, leaving ISCs as the predominant deformed cell, whereas in other capillary beds vaso-occlusion could be effected by both ISCs and other sickled cells, which, although capable of unsickling in the presence of high oxygen tensions, remain deformed at tensions and conditions operative in that capillary bed.

Failure to find a correlation between macular vascular changes and visual acuity reflects partly the mild degree of macular vascular damage in this small sample of patients but also the effects of causes of impaired visual acuity unconnected with macular disease, and possibly also a relative insensitivity in tests of visual acuity. Scores with the Arden gratings varied widely at all ages and in both ISC groups, and fell outside the presumed normal range in over half of this patient group. It is unlikely that these high scores indicate difficulties in communication, understanding, or technical performance of the tests, since satisfactory results have been obtained in population studies in other developing countries.[6] The frequency of high scores with the Arden gratings may reflect a real decrease in contrast sensitivity in this sample of patients with SS disease, and this is supported by the normal scores obtained in a small comparison group with a normal haemoglobin (AA) genotype. These observations are very preliminary, however, and require further study in large groups of patients and normal people carefully matched for as many determinants as possible.

This study was supported in part by a grant from the Midwest Association for Sickle Cell Anemia (MASCA).

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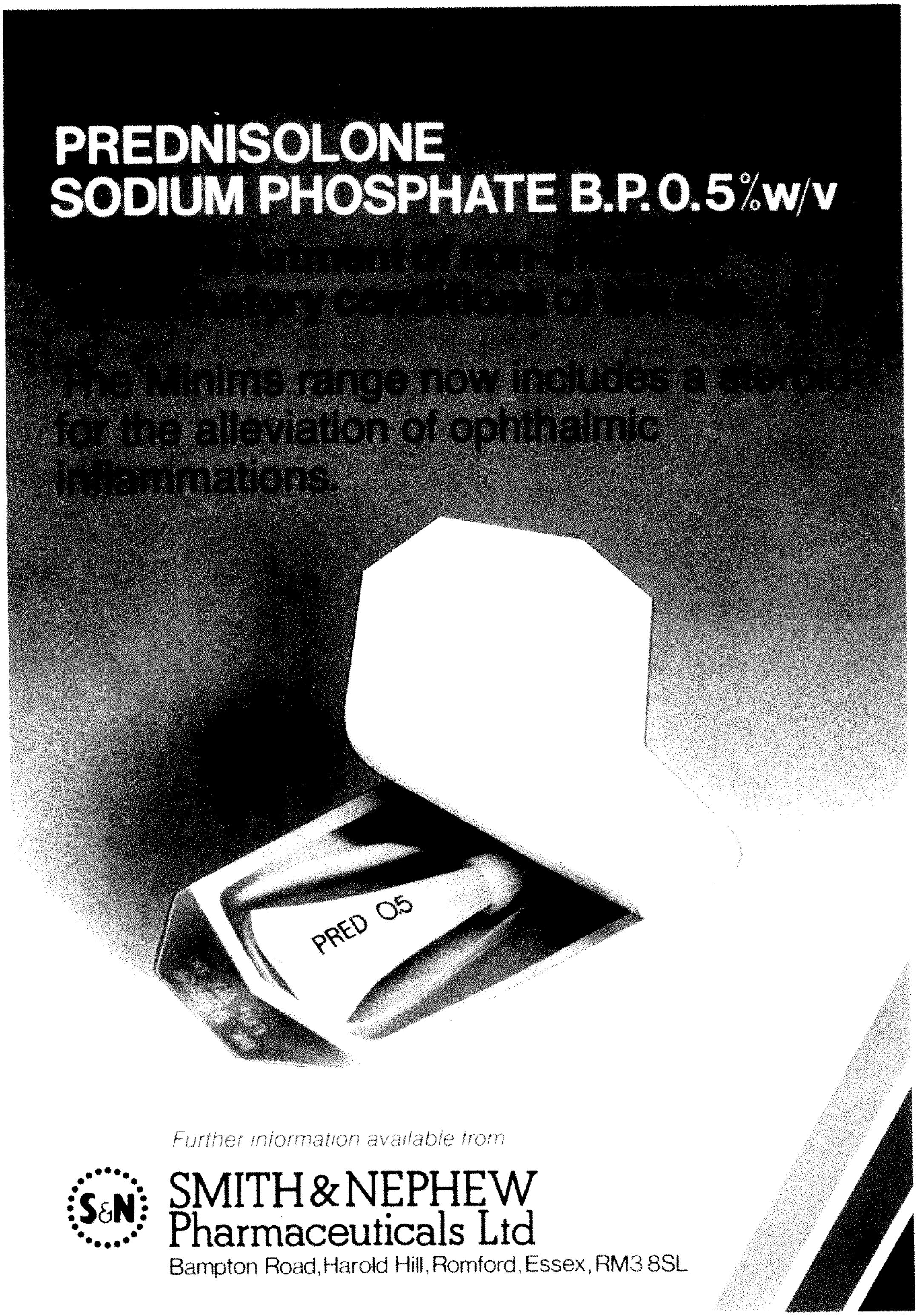

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Retinal vein occlusion and the prevalence of lipoprotein abnormalities

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SUMMARY Ninety-nine patients with retinal vein occlusion (40 with central, 59 with branch vein occlusion) were investigated for the prevalence of associated diseases for comparison with an age-matched control group. There was a significantly increased prevalence of hyperlipidaemia ($p<0\cdot001$) and hypercholesterolaemia ($p<0\cdot001$) in the group with branch retinal vein occlusion and of hyperlipidaemia ($p<0\cdot001$) and hypercholesterolaemia ($p<0\cdot02$) in the group with central retinal vein occlusion compared with controls. An increased prevalence of hypertriglyceridaemia ($p<0\cdot001$) was also found in patients with central vein occlusion. Other associations were noted (hypertension and oestrogen therapy). Increased serum cholesterol concentrations were found in patients with central vein occlusion ($p<0\cdot05$) and branch vein occlusion ($p<0\cdot001$) compared with controls, and similar tendencies were noted for levels of LDL and HDL cholesterol. Patients with central vein occlusion also had raised levels of serum triglyceride ($p<0\cdot001$) and VLDL-triglyceride ($p<0\cdot05$). The occurrence of both central and branch vein occlusions may be associated with an increased prevalence of hyperlipidaemia and hypertension. Increase of serum lipids may contribute to the aetiology of vein occlusion by altering plasma viscosity or affecting platelet function.

Occlusion of the retinal veins (either branch or central) is an important cause of visual loss, particularly in middle age.[1] Although the cause of this condition is unclear, it is frequently found in association with other diseases, such as hypertension or diabetes mellitus. Several recent studies have suggested that retinal vein occlusion may also occur more frequently in patients with hyperlipidaemia. For example, there was a 2- to 4-fold greater prevalence of hypercholesterolaemia or hypertriglyceridaemia in a group of 116 patients with central retinal vein occlusion than in a control population taken from published reports.[2] Possible explanations for the association of retinal vein occlusion with hyperlipidaemia may be through effects on plasma viscosity or alterations in platelet function, with release of platelet-specific proteins (B-thromboglobulin and platelet factor 4), thereby predisposing to platelet aggregation and thrombosis. These possibilities are of course not exclusive.

However, not all lipoprotein fractions have similar effects on vascular disease. Epidemiological studies have suggested that high-density lipoprotein (HDL) cholesterol may protect against macrovascular disease, whereas low-density lipoprotein (LDL) cholesterol may predispose to it.[3,4] Similar consideration may also apply to lipoproteins and microvascular disease.

For this reason we have studied individual lipoprotein fractions, with other possible predisposing factors, in a group of patients with retinal vein occlusion for direct comparison with an age-matched population.

Patients and methods

Ninety-nine patients with retinal vein occlusion (40 with central retinal vein occlusion and 59 with branch retinal vein occlusion) were investigated serially with no prior selection at Moorfields Eye Hospital. The diagnosis of retinal vein occlusion, apart from suggestive clinical history and funduscopy, was confirmed by fluorescein angiography. Further clinical examination included a search for the presence of large-vessel disease (angina, claudication, cerebrovascular accidents, and transient ischaemic attacks), alcohol consumption, smoking habits, and associated

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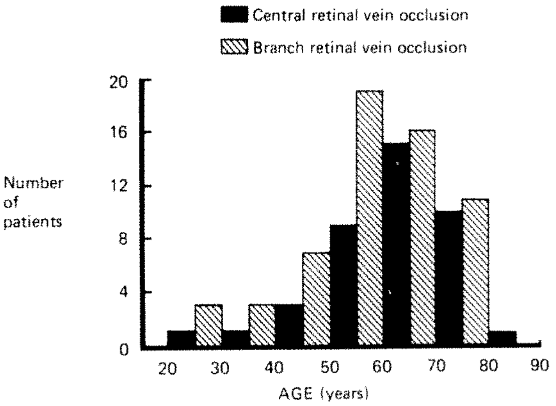

Fig. 1 *Age distribution of 99 patients presenting with retinal vein occlusion.*

drug therapy. After full clinical examination (by P.M.D.) the following investigations were performed: oral glucose tolerance test with a 75 g load, liver function tests, full haematological profile, plasma viscosity, electrocardiography, and chest radiology.

The comparison group for this study was recruited from hospital outpatients attending our clinics with treated essential hypertension (n=33) and hospital staff (n=7) who had no evidence of retinal venous occlusion. The same investigations were performed as in the group with retinal vein disease except for a full glucose tolerance test, where blood glucose estimations were taken with the fasting lipid profile.

Glucose intolerance and diabetes mellitus were diagnosed by the criteria of the British Diabetic Association recommendations.[5] Hypertension was defined as 3 consecutive blood pressure recordings of systolic greater than 160 mmHg and diastolic greater than 95 mmHg or when a patient was already established on antihypertensive drug therapy.

Plasma viscosity was measured by a Coulter-Harkness viscometer at 25°C (normal range 1·60-1·9 centipoise).[6] The electrocardiograms were coded and analysed for ischaemic heart disease, left ventricular hypertrophy, and bundle branch block by the Minnesota code.

Serum cholesterol and triglyceride concentrations were measured by semiautomated fluorimetric techniques (Technicon Instruments Co. Ltd.), Liebermann-Burchard's reagent being used for cholesterol (normal range: 4·5-6·7 mmol/l) and Cramp and Robertson's method for triglyceride (normal range: male, 0·6-2·1, female 0·6-1·8 mmol/l).[7] HDL cholesterol was measured in the supernatent fraction following precipitation of very low-density lipoprotein (VLDL) and LDL by heparin (250 units/50 μl) and 1 M manganese chloride (50 μl). VLDL cholesterol and triglyceride was measured after precipitation by sodium dodecyl sulphate (100 g/l in 0·15 M sodium chloride; 75 μl). LDL cholesterol was obtained by subtracting the sum of HDL and VLDL cholesterol from the total serum cholesterol.

The fluorescein angiograms of 33 patients with branch retinal vein occlusion were scored in single-blind manner for severity of capillary leakage, closure, and the presence of neovascularisation into 4 categories (nil=0, mild=1, moderate=2, severe=3, by A.M.H.) giving a measure of the severity of the retinal vein occlusion (range 1 to 10). Statistical analyses were performed by nonparametric tech-

Table 1 *Clinical and biochemical details of patients with retinal vein occlusion and the control group*

	Sex	*Mean age (yr)*	*Mean ideal weight (%)*	*Mean blood pressure (mmHg)*		*Mean fasting blood glucose (mM)*	*Mean serum cholesterol (mM)*	*Mean serum triglyceride (mM)*	*LDL cholesterol (mM)*	*HDL cholesterol (mM)*	*VLDL triglyceride (mM)*	*Plasma viscosity (centipoise)*	*Number of patients with ischaemic heart disease on ECG*	*Number of smokers*
				Systolic	*Diastolic*									
Control (n=40)	M30 F10	52·2 ±13·4	113·3 ±14·4	147·4 ±22	90·5 ±14·2	5·73 ±2·1	5·2 ±1·36	1·33 ±0·52	3·32 ±1·32	1·20 ±0·52	0·50 ±0·42	1·73 ±0·09	10 (25%)	12 (30%)
Central retinal vein occlusion (n=40)	M25 F15	62·6 ±11·2	111·7 ±13·8	157·7 ±31·5	87·6 ±11·5	5·7 ±1·8	5·64* ±1·61	1·62*** ±1·03	3·58 ±1·33	1·35 ±0·50	0·58* ±0·4 (n=38)	1·72 ±0·1	12 (30%)	13 (32·5%)
Branch retinal vein occlusion (n=59)	M39 F20	58·3 ±13·3	111·8 ±14·2	161·4*** ±30·3	91·6 ±17·5	5·1 ±1·1	6·0*** ±1·6	1·35 ±0·8	3·84** ±1·55 (n=57)	1·5** ±0·57	0·59 ±0·69 (n=51)	1·70 ±0·09	17 (29%)	25* (42·4%)

Values are mean±SD. *$p<0·05$. **$p<0·01$. ***$p<0·001$. Statistics by chi-squared test.
HDL=high-density lipoprotein. LDL=low-density lipoprotein. VLDL=very low-density lipoprotein.

niques (chi-squared test, binomial p test),[8] and correlations were made by the Pearson linear correlation coefficient.

Results

The mean age of onset of both branch and central retinal vein occlusion (55-65 yr) was similar and is presented in Fig. 1. Table 1 presents the mean serum lipids, lipoproteins, and other variables of the 3 groups under study. Higher serum cholesterol concentrations were found in patients with central retinal vein occlusion ($p<0{\cdot}05$) and branch retinal vein occlusion ($p<0{\cdot}001$) than in the control group and similar tendencies were noted for the levels of LDL and HDL cholesterol. Patients with central retinal vein occlusion also had raised levels of serum triglyceride ($p<0{\cdot}001$), but this was not so marked when VLDL triglyceride was measured.

The prevalence of macrovascular disease, as recorded by evidence of ischaemic heart disease on the electrocardiograph, was similar among the groups studied, but the patients with branch retinal vein occlusion had a higher mean systolic blood pressure ($p<0{\cdot}001$) than other groups.

The prevalence of other diseases associated with retinal vein occlusion is presented in Table 2. There was a significantly higher prevalence of hyperlipidaemia ($p<0{\cdot}001$) and hypercholesterolaemia ($p<0{\cdot}01$) in both retinal vein occlusion groups than in the comparison group. However, an increased prevalence of hypertriglyceridaemia ($p<0{\cdot}001$) was also found in patients with central retinal vein occlusion. Unfortunately it was not possible to compare the prevalence of hypertension in the retinal vein occlusion groups with that of the control group, as the latter were mainly drawn from a hypertension clinic (see 'Methods'). However, 41 out of 99 patients with retinal vein occlusion were found to have essential hypertension. Retinal vein occlusion was the clinical presentation in 16 patients with previously undiagnosed hypertension and in 25 with established hypertension on drug therapy. Systolic blood pressure was significantly higher ($p<0{\cdot}001$) in the established hypertensive patients on drug therapy (176·8±27·7 mmHg) and in the previously undiagnosed hypertensive patients (193·1±19·6 mmHg) than in the treated hypertensives in the comparison group (152·3±20·5 mmHg, n=33). It was also of interest that 4 patients presenting with retinal vein occlusion (2 with central and 2 with branch retinal vein occlusion) were taking oestrogen therapy, one patient was on an oral contraceptive, and 3 were on oestrogen therapy for post-menopausal symptoms when they presented at our clinic.

Table 2 *Prevalence of associated diseases in retinal vein occlusion*

Associated disease	*Comparison group (n=40)*	*Branch retinal vein occlusion (n=59)*	*Central retinal vein occlusion (n=40)*
Hyperlipidaemia	15% (6)	28·8% (17)**	32·5% (13)**
Hypercholesterolaemia	7·5% (3)	23·7% (14)**	22·5% (9)*
Hypertriglyceridaemia	7·5% (3)	8·5% (5)	25% (10)**
Hypertension	82·5% (33)	44% (26)	37·5% (15)
Diabetes mellitus	9·5% (4)	10% (6)	15% (6)
Glucose intolerance	—	15·3% (9)	17·5% (7)
Oestrogen therapy	—	3·4% (2)	5% (2)
No associated disease or drug therapy	—	37·3% (22)	22·5% (9)

*$p<0{\cdot}02$, **$p<0{\cdot}001$ by nonparametric statistics (chi-squared and binomial p test).

There were no significant differences in the mean plasma viscosities of the 3 groups studied as shown in Table 1. However, the association of raised levels of cholesterol, triglyceride, and LDL cholesterol with retinal vein occlusion may be related to alterations in the plasma viscosity, as shown by the correlations found between these parameters in Table 3. Total serum proteins and serum globulins were positively correlated with plasma viscosity ($p<0{\cdot}001$), but weaker positive correlations were found with total serum cholesterol ($p<0{\cdot}01$), LDL cholesterol ($p<0{\cdot}01$), VLDL cholesterol ($p<0{\cdot}05$), and total serum triglyceride ($p<0{\cdot}05$). A significant positive correlation was also found in patients with branch retinal vein occlusion between the fluorescein score and serum LDL cholesterol levels ($r=+0{\cdot}492$, $n=33$, $p<0{\cdot}01$) and a weaker correlation with total serum cholesterol ($r=+0{\cdot}39$, $n=33$, $p<0{\cdot}05$).

Table 3 *Linear correlation coefficients between serum lipid parameters, serum proteins with plasma viscosity in patients with retinal vein occlusion*

		Total serum cholesterol (mM)	*Total serum triglyceride (mM)*	*LDL cholesterol (mM)*	*VLDL cholesterol (mM)*	*Serum globulins (g/l)*	*Serum total proteins (g/l)*
Plasma viscosity (centipoise)	Correlation coefficient	0·297	0·230	0·277	0·223	0·601	0·36
	Number of patients	99	99	97	97	90	91
	Significance	<0·01	<0·05	<0·01	<0·05	<0·001	<0·001

Discussion

Our results suggest that hyperlipidaemia is more likely to occur in patients with retinal vein occlusion than in an age-matched comparison group. Serum cholesterol and LDL cholesterol showed a stronger association with retinal vein occlusion than serum triglyceride or VLDL triglyceride. However, mean serum HDL cholesterol concentrations were higher in the branch retinal vein occlusion group ($p<0\cdot01$) but were also raised in patients with central retinal vein occlusion. HDL lipoprotein can be fractionated into 2 components, HDL-2 and HDL-3, with different lipid and apoprotein compositions. It has previously been shown that the HDL-2 subfraction related more strongly to the occurrence of large-vessel disease,[9] and it is possible that subfractions of HDL may show stronger associations with microvascular disease, such as retinal vein and arteriolar occlusions, than total HDL cholesterol.

Of the other associated factors smoking habits, frequency of large-vessel disease, and glucose intolerance may also be determinants, though only minor differences were observed between the retinal vein occlusion and control groups.

Systolic blood pressure in patients with branch retinal vein occlusion was significantly higher than in the comparison group, who were predominantly treated essential hypertensives. This suggests that hypertension may be a major aetiological factor. It is further supported by the high prevalence of hypertension in our patients with branch retinal vein occlusion and by the finding of left ventricular hypertrophy in 6 of the 26 hypertensive patients with branch retinal vein occlusion, compared with only 2 of the 33 hypertensive patients in the comparison group. Systolic blood pressure was also raised in patients with established hypertension on drug therapy. There was also a higher incidence of hypertension in patients with central retinal vein occlusion (37·5%) than that quoted in the normal population (for example, 21·2%).[10]

The pathogenesis of retinal vein occlusion is still in dispute. Possible aetiological factors include venous thrombosis or endothelial swelling and constriction, which may predispose to microvascular thrombosis.[11] Ring *et al.*[12] have also suggested that whole blood viscosity may be a contributory factor, as they found a close correlation between the whole blood viscosity and the severity of retinal ischaemia on fluorescein angiography in patients with branch and central retinal vein occlusion.

There were no statistical differences in the mean plasma viscosities among the groups studied, but there was a significant correlation between plasma viscosity and plasma lipids, particularly total and LDL cholesterol, which, like serum globulins and total proteins, clearly contribute to the plasma viscosity and, if increased, may predispose to a 'hyperviscosity' syndrome. LDL cholesterol and total serum cholesterol were also significantly correlated with the fluorescein score, which gives a measure of the severity of the retinal vein occlusion. These results in conjunction with the significantly raised serum LDL cholesterol and total serum cholesterol suggest that the major cholesterol-containing lipoproteins may contribute to the pathogenesis of retinal vein occlusion. Alternative explanations such as the effects of lipoproteins on the platelet release reaction that predisposes to aggregation are under current investigation in our laboratory.

We conclude therefore that both central and branch retinal vein occlusion are associated with an increased prevalence of hyperlipidaemia, hypertension, and glucose intolerance. Total serum cholesterol and LDL cholesterol are raised in patients with retinal vein occlusion and may contribute to the aetiology of this condition. HDL cholesterol levels are higher than in the comparison group and do not appear to be protective for the retinal microcirculation. Any patients with retinal vein occlusion should be investigated for underlying hypertension, hyperlipidaemia, and diabetes mellitus and appropriate therapy instituted.

Financial assistance to P.M.D. from the Area Health Authority (T) and Joint Research Board of St Bartholomew's Hospital is gratefully acknowledged.

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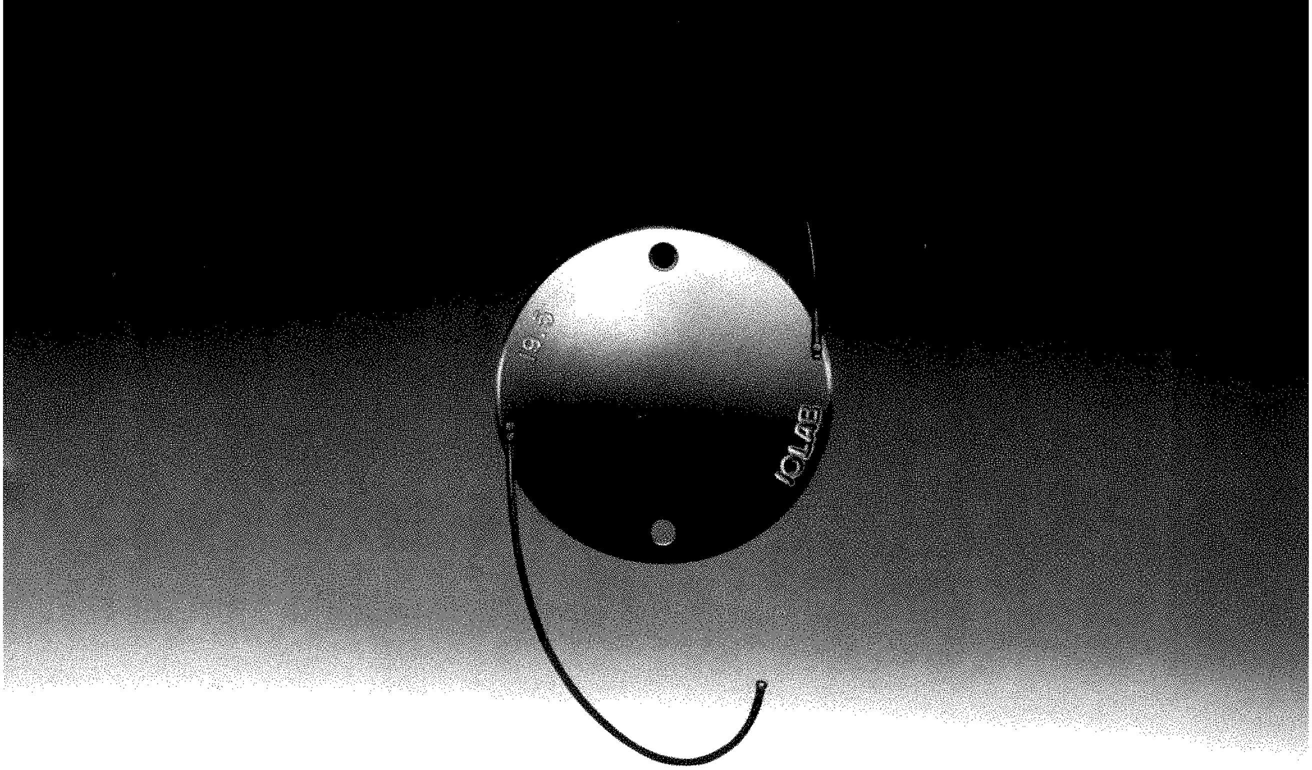

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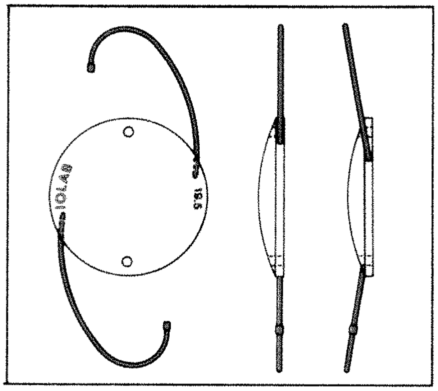

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British Journal of Ophthalmology, 1982, **66**, 165–169

A low-molecular-weight angiogenic factor in cat retina

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SUMMARY A low-molecular-weight angiogenic factor has been isolated from healthy adult cat retinas. The factor, which has been purified by diethylaminoethyl (DEAE) cellulose chromatography and affinity chromatography, stimulates neovascularisation of the chick chorioallantoic membrane and has a number of properties similar to those previously described for a tumour factor. The finding of an angiogenic factor in healthy retina and its relationship to previously described inhibitors of angiogenesis is discussed.

Retinal neovasularisation can be a serious complication in a number of ocular disorders.[1 2] The observation that retinal capillary malperfusion often precedes neovascularisation[3-5] and furthermore that destruction of the areas of nonperfused retina results in regression of the newly formed vessels[6 7] has suggested that a diffusable substance with vasoproliferative properties may be formed by the ischaemic retina. Direct evidence for a retina-derived angiogenic factor has recently been reported. Federmann *et al.*[8] observed the growth of limbal vessels toward implants of retinal tissue in rabbit corneas, and other workers[9-13] have demonstrated the presence of angiogenic activity in extracts of retinal tissue.

In this report we describe the purification of a factor from feline retina which in a crude form has been shown to stimulate growth of the limbal vessels into the rabbit cornea.[9] Preliminary studies indicate that the factor has a low molecular weight and resembles a factor isolated from rat Walker 256 tumours[14 15] and from the synovial fluid of diseased joints.[16]

Materials and methods

Adult cats aged 4–6 years from the Institute of Ophthalmology colony were used in these studies. They were administered an overdose of pentobarbital (Sagatal), and the eyes were enucleated when the animals were under deep anaesthesia. The retinas were removed immediately under sterile distilled water at 4°C. Batches of 8 retinas were pooled and stored at −40°C.

The retinas (1 batch, 8 retinas) were thawed and homogenised for 1 minute at 4°C in a glass Potter-Elvehjem homogeniser. The homogenate was incubated at 4°C for 30 minutes and then spun at 600 *g* for 15 minutes at 4°C. The supernatant was collected and the pellet re-extracted as described above. Both supernatants were pooled and spun at 100 000 *g* for 1 hour at 4°C, when the clear supernatant was decanted and purified by diethylaminoethyl (DEAE) cellulose column chromatography and by affinity chromatography using a modification of the method described for the purification of a tumour angiogenic factor.[14]

DEAE CELLULOSE CHROMATOGRAPHY

Solid ammonium bicarbonate was added to the 100 000 *g* supernatant to give a final concentration of 50 mM salt. This sample was applied to a column (8×1 cm) of DEAE cellulose (Whatman) equilibrated with 50 mM NH_4HCO_3 (pH 7·9) at 4°C. Unbound material was eluted with the same buffer at a flow rate of 50 ml/h. The column effluent was monitored at 280 nm (Uvicord S, LKB, Sweden) and 14 ml fractions were collected. Bound material was eluted with a convex salt gradient (0–0·3 M NaCl) prepared in a constant level mixing device from 50 mM NH_4HCO_3 (65 ml) and 50 mM NH_4HCO_3 (100 ml) containing 0·3 M NaCl. The column was finally washed with 50 mM NH_4HCO_3 containing 0·5 M NaCl.

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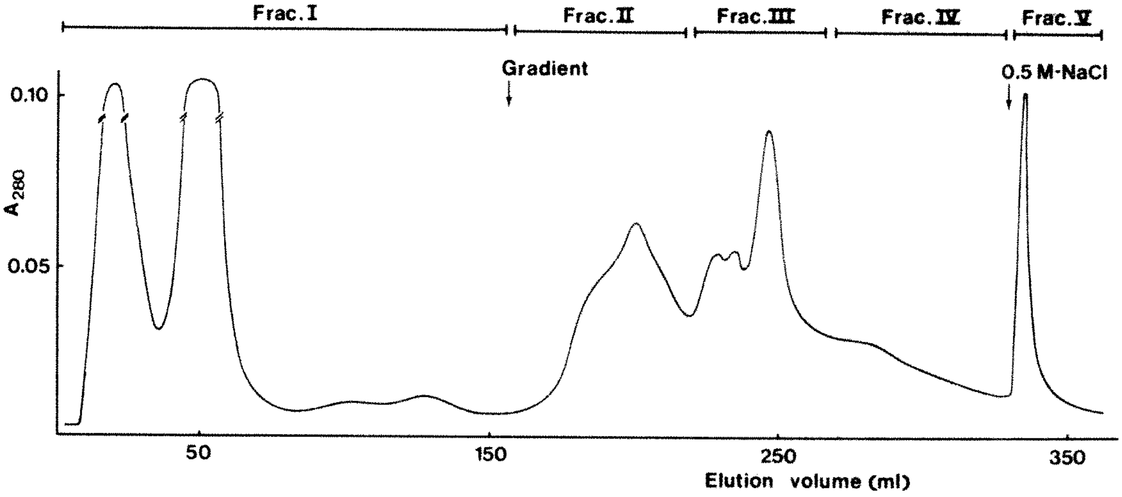

Fig. 1 *DEAE cellulose chromatography of retinal homogenate.*

AFFINITY CHROMATOGRAPHY

Fractions corresponding to regions I–V of the DEAE cellulose column elution profile (Fig. 1) were pooled and purified by affinity chromatography. An antibody prepared against tumour-derived angiogenic factor[17] was bound to cyanogen bromide activated Sepharose 4B (Pharmacia, Uppsala, Sweden) (10 mg of IgG to 1 g dry Sepharose 4B), and a column of the affinity absorbent was prepared (3×1 cm) and equilibrated with 50 mM NH_4HCO_3 containing 0·5 M NaCl at 4°C. Fractions I–V were pumped separately on to the affinity column (30 ml/h), and unbound material was eluted in each case with the same buffer. Specifically bound material was eluted with 50 mM acetic acid adjusted to pH 3·5 with 0·880 ammonia. The column effluent was monitored at 280nm, and 1 ml fractions were collected.

Extracts of feline iris and rat liver were also prepared by the method described for the feline retina. In a further control experiment a sample of 50 mM ammonium bicarbonate buffer (8 ml) was chromatographed on the DEAE cellulose and affinity columns.

Fractions were assayed for angiogenic activity by the chick chorioallantoic membrane (CAM) assay system previously described.[14 17] Samples for assay

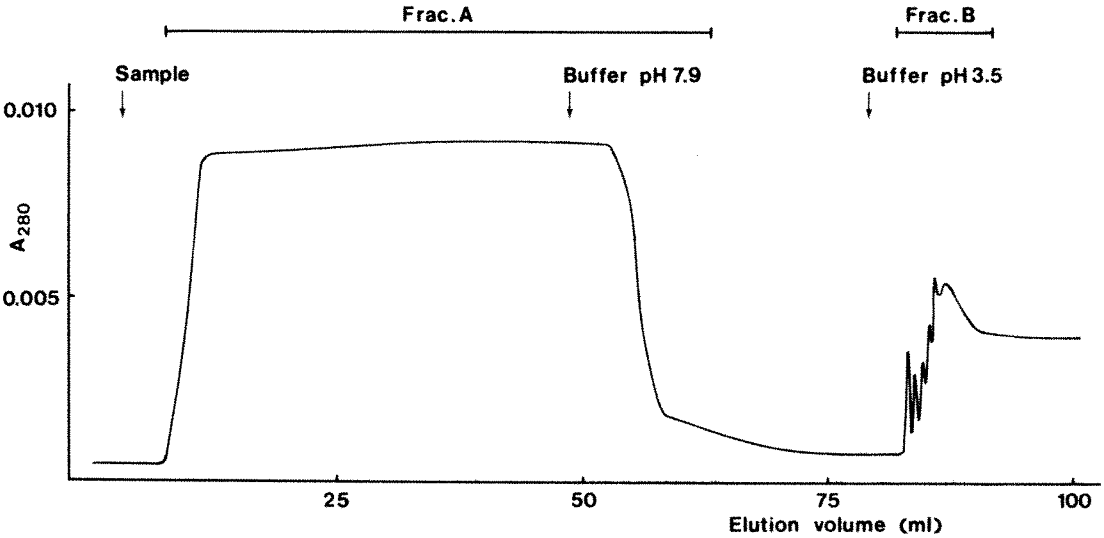

Fig. 2 *Affinity chromatography of retinal extract.*

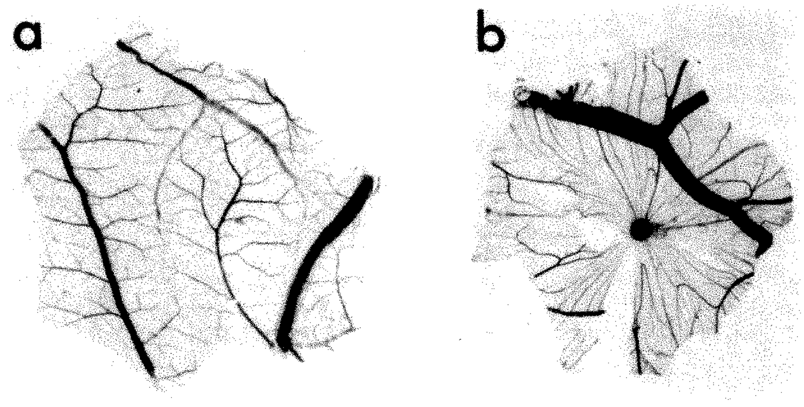

Fig. 3 *Chick chorioallantoic membrane showing a control* (a) *and test* (b).

were sterilised by filtration through a 0·22 μm membrane and freeze-dried before application to the CAM.

Results

A typical DEAE cellulose chromatography elution profile is shown in Fig. 1. Fraction I contained material unbound by the DEAE cellulose, fractions II–IV contained material eluted by a convex gradient of 0–0·3 M NaCl, and fraction V contained material eluted by a 0·5 M NaCl wash. Angiogenic activity was identified by the CAM assay technique and was detected in fractions IV and V. Material from the unbound peak (fraction I) did not give a positive angiogenic response on the CAM.

Fractions I–V were further purified by affinity chromatography using Sepharose-bound antibody raised against a tumour-derived angiogenic factor. Unbound material was contained in fraction A (Fig. 2) and specifically bound material in fraction B. The majority of the 280 nm absorbing material was not bound to the affinity column. The small irregular peak corresponding to fraction B (Fig. 2) was caused by the mixing of the washing buffer pH 7·9 and the eluting buffer pH 3·5. The elevated base line after fraction B was due to the absorbance of the 50 mM ammonium acetate buffer. The presence of angiogenic factor in fraction B could be detected only by the biological assay, as no detectable change attributable to the factor occurred in the recorder trace at 280 nm.

Those fractions that were initially positive after chromatography on DEAE cellulose always gave a positive fraction B after affinity chromatography, whereas those fractions that were initially negative from DEAE cellulose chromatography did not give a positive fraction B. No fractions from DEAE chromatography of a buffer control and extracts of feline iris and rat liver prepared by the method described above induced neovascularisation of the CAM either before or after affinity chromatography.

A typical chorioallantoic membrane response to a sample of retina-derived angiogenic factor is shown in Fig. 3. The positive reaction in Fig. 3b involves the bending in of medium sized vessels and the spoke-wheel appearance of small vessels growing towards the point of sample application. No such directional growth can be seen on the control membrane (Fig. 3a).

Active freeze-dried material from an affinity column was dissolved in 50 mM NH_4HCO_3 (5 ml) and dialysed against 50 mM NH_4HCO_3 (5 ml) at 4°C for 2 hours. After freeze drying the diffusate and retentate were both found to contain angiogenic activity when tested on the CAM, indicating that the active component was freely diffusible.

Discussion

A low-molecular-weight factor that stimulates neovascularisation of the chick CAM has been purified from the retinas of healthy adult cats. The factor resembles a low-molecular-weight tumour angiogenic factor previously described.[14] Both factors are anionic as indicated by their binding to DEAE cellulose and are also eluted from the DEAE cellulose by a similar concentration of sodium chloride, indicating a comparable charge density. The retina angiogenic factor and the tumour factor give similar reactions on the chick chorioallantoic membrane and appear to be antigenically similar, as they both bind specifically to an antibody raised against the tumour factor. After purification by affinity chromatography both factors are dialysable. The crude tumour factor is non-dialysable after chromatography on DEAE cellulose but becomes freely dialysable after affinity chromatography. It is presumed that the crude tumour factor is associated with a high-molecular-weight carrier molecule which gives it an apparent molecular weight far in excess of that for the purified material.[14–18] The same appears to be true for the retina angiogenic factor. Again it is not until after the affinity chromatography step that the factor becomes dialysable. This suggests that the active component is separated from a carrier protein complex during the affinity procedure.

The feline retina angiogenic factor has a number of of properties similar to those described by D'Amore *et al.*[13] for bovine retina angiogenic factor. Both factors stimulate neovascularisation of the chick CAM and both are bound by DEAE cellulose. However, the factor described by D'Amore *et al.* has a relatively high molecular weight, and treatment with a number of dissociating reagents, including ethanol, used previously to purify a low-molecular-weight angiogenic factor from tumours, failed to reduce the molecular weight of their active retinal material. The extraction procedure used in this work, homogenisation followed by incubation at 4°C, may be a more effective preparative method than incubation alone as used by D'Amore *et al.* Possibly the bovine retinal factor exists solely as a high-molecular-weight molecule. However, it may be that binding of the retinal factor by the antibody weakens the carrier-angiogenic factor interaction more effectively and that this treatment has allowed the preparation of a low-molecular-weight material. On the other hand Chen and Chen[10] reported the isolation of an angiogenic factor which they described as 'a small molecule' from the retina of a number of mammalian species including bovine.

The findings in the present study indicate that angiogenic activity is present in healthy retina. A possible explanation for the absence of preretinal neovascularisation in the healthy state is that the vitreous, which is normally avascular, has been shown to contain substances that will inhibit the growth of new blood vessels.[19–21] Such inhibitors may be involved in controlling the activity of any retinal angiogenic factor. This does not of course preclude the possibility that the retina itself contains inhibitors as well as activators of angiogenesis.

Henkind[2] has emphasised from careful clinical observations that retinal neovascularisation requires both an abnormal retinal vascular bed (diseased vessels) and an embarrassed (hypoxic) sensory retina. Furthermore he suggests that if perfusion is relatively normal the retinal vessels will not proliferate in spite of the presence of angiogenic substances.

The primary events therefore in the initiation of new blood vessel growth may not necessarily involve increased production of angiogenic factor(s). If both activator and inhibitor are present at equilibrium in the normal retina, in the ischaemic retina there may be a loss of inhibitor rather than an increase in angiogenic factor, particularly if the activating substance is a low-molecular-weight compound and therefore possibly not susceptible to degradation by lysosomal enzymes. Consequently it is reasonable to assume that this relative increase in activator may stimulate neovascularisation. The demonstration of appreciable amounts of angiogenic factor in healthy feline retina would support this contention.

The question whether tumour angiogenic factor and retinal angiogenic factor are identical requires further research, although their similar antibody binding affinities suggests a close resemblance. It also needs to be established whether different workers are describing the same or different factors. Both these questions should be answered when precise structural characterisation has been achieved.

This work was supported in part by grants from the Arthritis and Rheumatism Council and the British Diabetic Association.

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British Journal of Ophthalmology, 1982, **66**, 170–173

Vitelliform macular dystrophy and butterfly-shaped epithelial dystrophy: a continuum?

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SUMMARY We report the case of a 22-year-old white female who presented for a routine ocular examination and displayed Best's disease in her right eye and butterfly-shaped macular dystrophy in her left eye. These diagnoses were confirmed by fluorescein angiography, EOG, and ERG. The fact that these 2 disorders are present in one person suggests that they are only different manifestations of the same underlying disease process.

Vitelliform macular dystrophy (Best's disease) and butterfly-shaped epithelial dystrophy of the macula (Deutman's dystrophy) have been described as 2 separate heredodystrophic diseases affecting the retinal pigment epithelium and the outer retina.[1 2] We report a patient who has vitelliform macular dystrophy (VMD) in the right eye and butterfly-shaped epithelial dystrophy (BED) in the left eye.

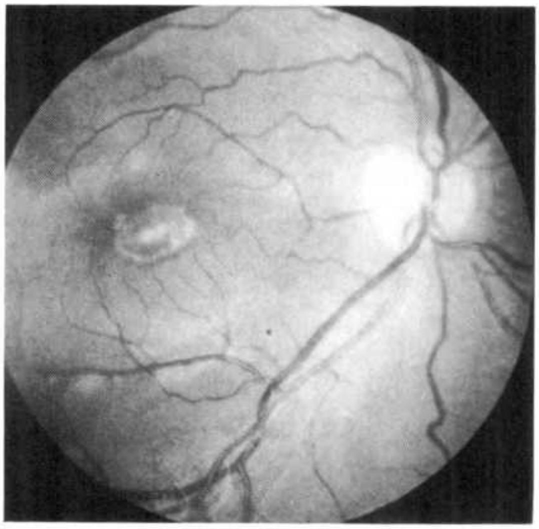

Fig. 1 *Fundus photograph OD: An oval, well-demarcated, yellowish, macular lesion, 3/4 disc diameter in size.*

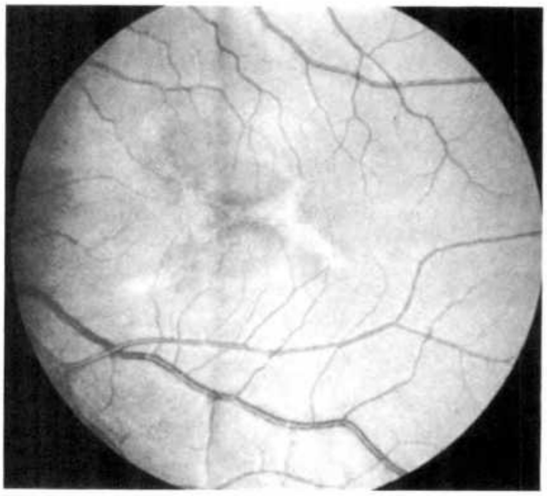

Fig. 2 *Fundus photograph OS: A butterfly-shaped, hyperpigmented lesion, about 3 disc diameters in size, in the macular region.*

This is the first case that suggests these 2 rare diseases may be different manifestations of the same heritable disorder.

Case report

The patient is a 22-year-old white female who presented to the eye clinic for a routine examination. She had no visual complaints. Medical and ocular histories were unremarkable. Ocular examination showed an uncorrected visual acuity of 6/6 (20/20)

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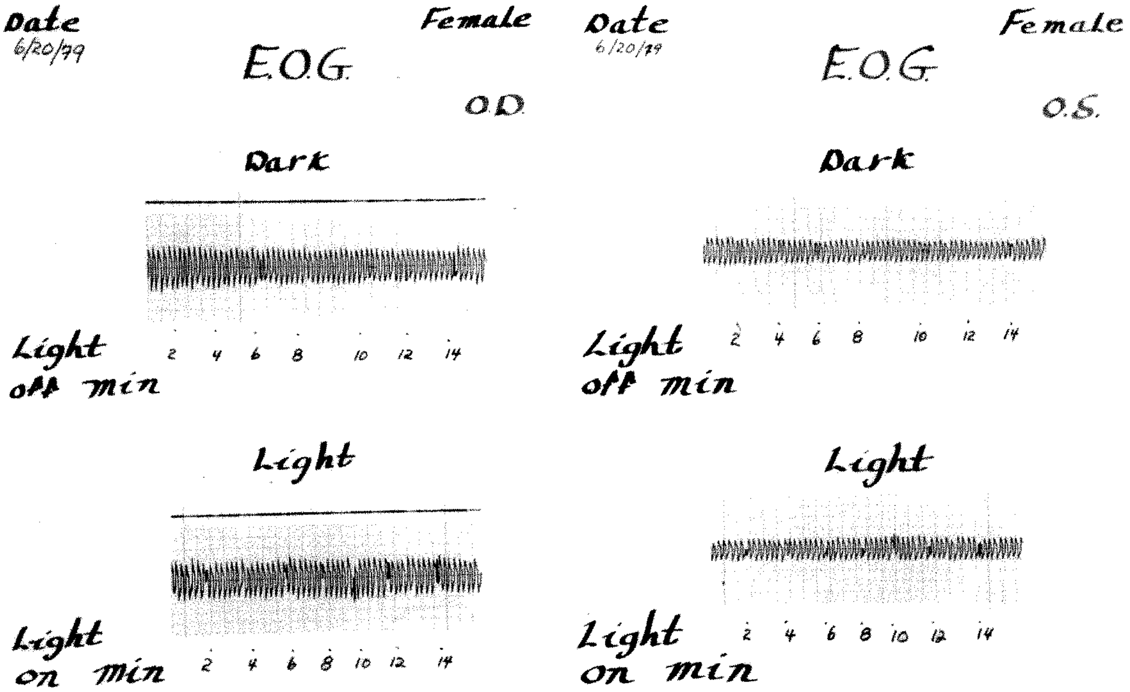

Fig. 3a

Fig. 3b

Fig. 3 *EOG shows no light rise: (a) OD, (b) OS.*

J1+ in each eye (OU), tension by applanation 16 mmHg, and ocular motility full OU. By slit-lamp biomicroscopy the lids, conjunctivae, and anterior segments were normal OU. Pupils were 2·5 mm, round, equal and had normal light and accommodative responses; lenses and vitreous bodies were clear OU. Examination of the fundi revealed normal discs, blood vessels, and periphery. The macula of the right eye showed a 3/4-disc-diameter oval, yellowish, well-demarcated lesion at the level of the retinal pigment epithelium (RPE) without visible alteration of the overlying retina (Fig. 1). The left macula showed a 3-disc-diameter, H-shaped, hyperpigmented lesion of the RPE with an intact overlying retina (Fig. 2).

Laboratory data: Visual fields (Goldmann)—full OU. Colour vision (American Optical-Hardy, Rand, and Rittler pseudoisochromatic)—normal OU. Amsler grid—normal OU. Electro-oculogram (EOG)—LP/DT:1/1 OU (Figs. 3a, 3b). Electroretinogram (ERG)—normal OU (Figs. 4a, 4b). Fluorescein angiography—blockage of background fluorescence in the area of RPE changes without leakage (Figs. 5a, 5b).

A 24-year-old sister had 6/6 (20/20) visual acuity OU and ophthalmoscopically had the clinical picture of an extrafoveal vitelliform dystrophy OU. No further diagnostic procedures were allowed, and other family members were not available for examination.

Discussion

Butterfly-shaped epithelial dystrophy of the macula (BED) is an extremely rare autosomal dominant disease, first described by Deutman *et al.*[2] They described a pedigree with affected members, 4 brothers and one son, all of whom had good visual acuity. By funduscopy the macular area showed a peculiar bilateral butterfly-shaped hyperpigmentation. These pigmentary changes appeared to be at the level of the RPE.

There are no clinicohistopathological correlations of this disease and the prognosis is unknown.

Vitelliform macular dystrophy (VMD) is an autosomal dominant macular disorder first described by F. Best in 1905.[1 3] Many cases have been recorded.

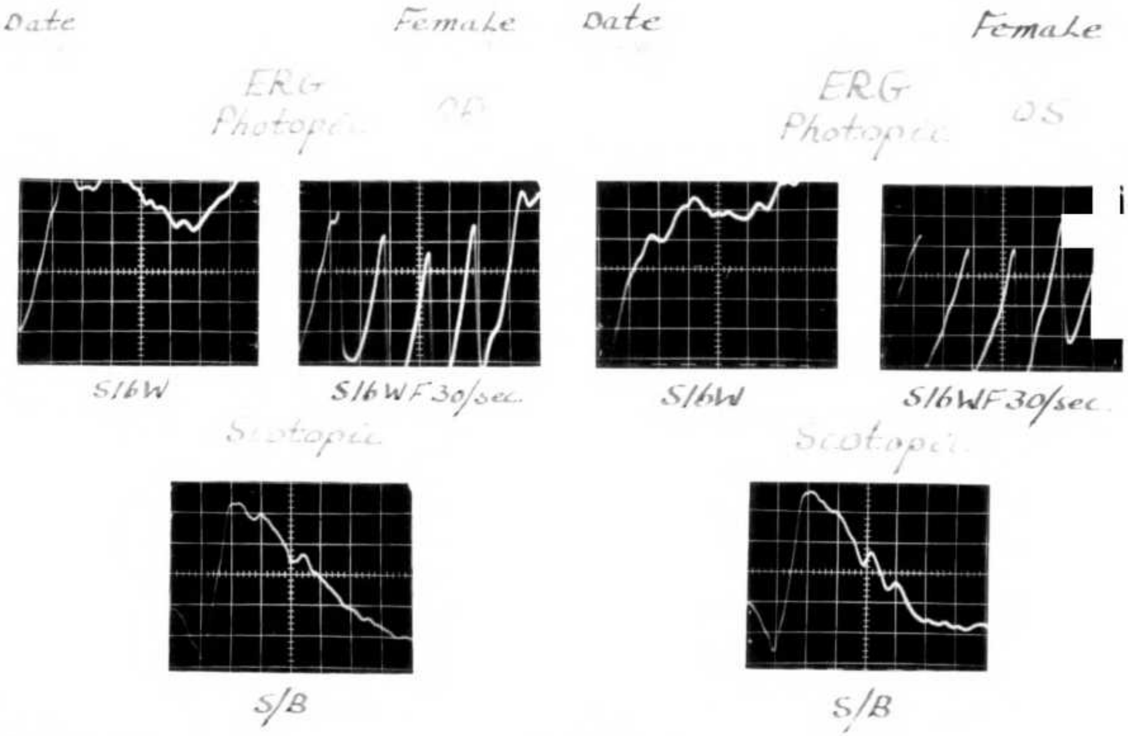

Fig. 4a Fig. 4b

Fig. 4 *ERG under standard conditions is normal: (a) OD, (b) OS. Recordings made using a Grass PS 22 Photostimulator. Photopic: single flash and flicker fusion at 30/s. Scotopic: recruitment response with a blue flash.*

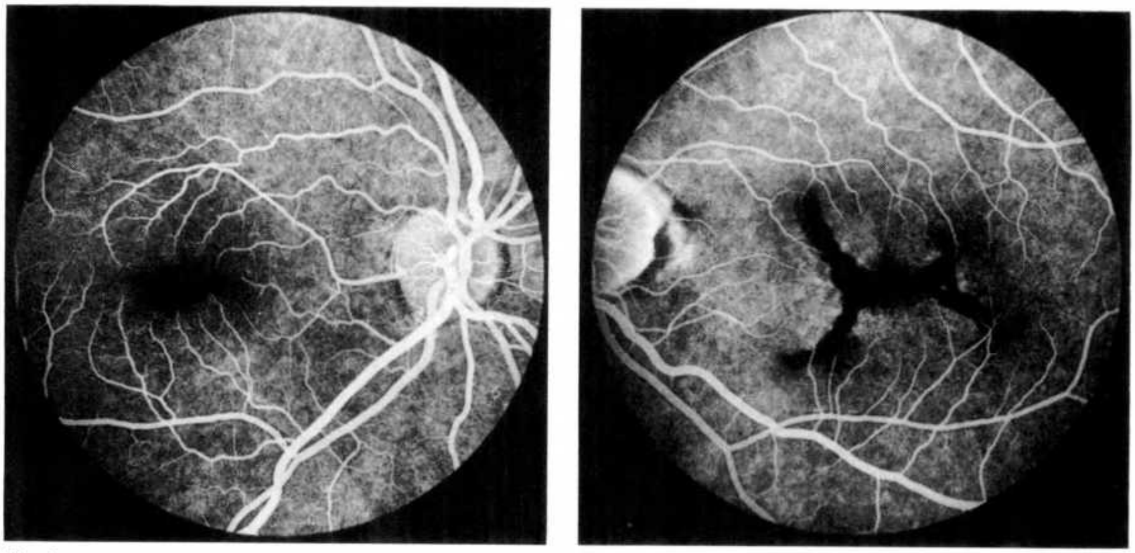

Fig. 5a Fig. 5b

Fig. 5 *Fluorescein angiogram in early venous phase shows blockage of background fluorescence in the area of the fundus lesion: (a) OD, (b) OS.*

Table 1 *Comparision of vitelliform macular and butterfly-shaped dystrophy*

	Vitelliform macular dystrophy	*Butterfly epithelial dystrophy*
Mode of inheritance	Autosomal dominant	Autosomal dominant
Visual acuity:		
(a) presentation	Normal	Normal
(b) follow-up	May diminish	Unknown
Colour vision:		
(a) presentation	Normal	Normal
(b) follow-up	May diminish	Unknown
Visual fields	Normal	Normal
Fluorescein angiography	Blockage of background fluorescence by the lesion	Blockage of background fluorescence by the hyperpigmented area
ERG	Normal	Normal
EOG	Abnormal	Abnormal

Ocular examination is normal except for funduscopy. Yellowish, oval, sharply demarcated 'cystic' lesions are seen bilaterally at the level of the RPE. They may be present at birth but are typically discovered between ages 3 and 15.[4] At the first stage of the disease the lesion is well demarcated and uniform in appearance, and the overlying retina appears normal. At this stage visual acuity is usually normal. This vitelliform 'cyst' may persist for a number of years but characteristically breaks up in the second or third decade. As it becomes less uniform and pigmentary changes occur, the lesion transforms from an 'egg-yolk' to a 'scrambled-egg' appearance, and visual acuity diminishes to between 20/50 and 20/200. Rarely, subretinal neovascularisation may occur, and macular scarring is the end stage.

At the 1980 meeting of the Association for Research in Vision and Ophthalmology Weingeist, Kotbrin, and Watzke presented the histopathology of a 29-year-old patient with VMD in the 'scrambled-egg' stage.[5] Light and electron microscopy indicated that VMD is a generalised retinal pigment epitheliopathy which results in abnormal accumulation of lipofuscin granules within the RPE.

VMD and BED were initially described as separate clinical entities. As more became known about them, some similarities have been noted.[6,7] The same is true for another group of diseases of the retinal pigment epithelium, including dystrophia reticularis, dystrophia macroreticularis, reticular pigment dystrophy, butterfly dystrophy, and fundus pulverulentus. In all of these entities the pathogenesis is unknown. The visual prognosis is good, and different patterns of these reticular pigmentations may be seen in the same family. These diseases have been included under the title of 'pattern dystrophies.' This term was coined independently by Hsieh *et al.*[6] and Marmor and Byers.[7]

There are similarities between VMD and BED upon testing (Table 1). In our patient BED and VMD are present in opposite eyes. This strongly suggests that VMD and BED may be different expressions of the same disease process. Proof of this hypothesis will depend on a careful examination of affected pedigrees and histopathological studies.

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British Journal of Ophthalmology, 1982, **66**, 174–178

Traumatic wound dehiscence following penetrating keratoplasty

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SUMMARY Four young male patients with keratoconus had traumatic dehiscence of the surgical wound after penetrating keratoplasty. Two were rendered aphakic by the trauma, and in one patient the lens was dislocated posteriorly. In each case the dehiscence was repaired by resuturing the original corneal graft. Despite marked corneal oedema in the immediate postoperative period all four grafts deturgesced and subsequently cleared. The follow-up has been a minimum of 23 months. We recommend therefore primary resuturing of traumatic wound dehiscence after keratoplasty, anterior vitrectomy if the lens is dislodged, and prophylactic antibiotics postoperatively. The clearing of the initially oedematous grafts in each case illustrates the resilience of the corneal endothelium.

Wound separations sometimes occur after penetrating keratoplasty, usually soon after suture removal.[1 2] Such wound dehiscences have been particularly associated with grafts for corneal oedema,[1 2] use of continuous-suture techniques,[2] and postoperative elevation of intraocular pressure (IOP).[1]

Friedman[3] reported keratoplasty wound dehiscence in 2 elderly aphakic ladies after severe, blunt ocular trauma 4 years and 6 years after transplant. In both cases the vision was no light perception, and enucleations were performed, revealing retinal detachment and massive intraocular haemorrhage. Binder *et al.*[1] mentioned a traumatic wound separation at 49 weeks after keratoplasty, and Polack and Binder[4] studied by scanning electron microscopy the transplanted cornea from a male with keratoconus who had a wound dehiscence after ocular trauma one week following suture removal. Raber *et al.*[5] recently reported 12 cases of traumatic wound dehiscence in 10 keratoplasty patients.

At the Wilmer Institute we followed up 4 patients who had undergone traumatic wound dehiscence sustained after penetrating keratoplasty. In each case the transplanted cornea was resutured in position, and each subsequently deturgesced completely. This series indicates that primary resuturing of corneal grafts after traumatic dehiscence is the preferred management of such cases.

Case reports

CASE 1

In 1968, at age 23, this male patient with bilateral keratoconus underwent penetrating keratoplasty in the right eye followed in 1969 by a penetrating keratoplasty in the left eye. Both eyes did well postoperatively until 29 November 1975, when he was struck in the left eye during a bar-room brawl. The corneal graft wound ruptured inferiorly, and the lens was expelled from the eye through the keratoplasty dehiscence. An anterior vitrectomy was performed, and the wound was repaired with interrupted 10-0 monofilament nylon sutures. In October 1977, 23 months after repair, the corrected visual acuity was 6/6 (20/20) in the involved eye, and the cornea was clear (Fig. 1).

CASE 2

On 28 July 1972, when he was aged 20, a 7·5 mm penetrating keratoplasty was performed with 10-0

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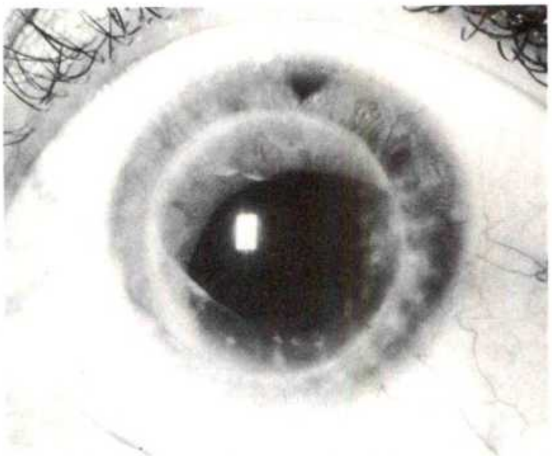

Fig. 1 *Four months after repair of sound rupture inferiorly the original graft is clear (case 1).*

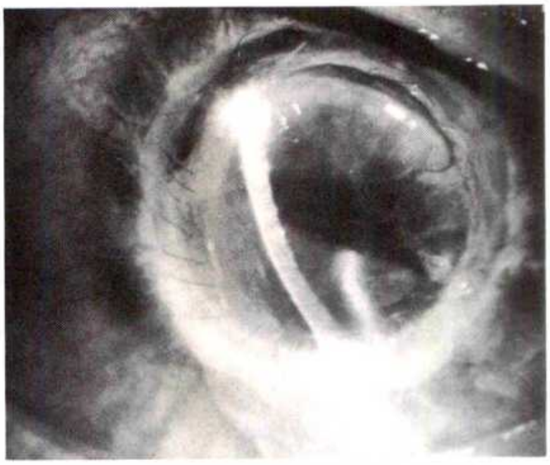

Fig. 2 *Iris tissue plugs the keratoplasty-wound dehiscence superiorly 3 days after injury by a champagne cork. Slit-beam shows thickening of the corneal button (case 2).*

monofilament nylon interrupted sutures on the patient's right eye for keratoconus. Best visual acuity obtained was 6/9 (20/30). About 10 weeks after keratoplasty he was struck in the operated eye by a Frisbee (a plastic disc thrown in a game). Experiencing immediate pain and decreased vision in the affected eye, he was examined immediately at the Wilmer Institute, where the vision was light perception without projection. The graft was found to be prolapsed and sandwiched between the eyelids but was anchored by 2 or 3 sutures in the inferonasal quadrant. By slit-lamp examination the opaque-appearing cornea was 3 times the normal thickness superiorly and twice the normal thickness inferiorly.

Because suitable donor corneal tissue was not immediately available, the surgeon elected to resuture the existing cornea to serve as a temporary covering graft. This was done with interrupted 10-0 monofilament nylon sutures. Postoperatively, however, the graft cleared slowly, and 29 months later the patient's visual acuity in the injured eye was 6/9 (20/30) with correction. The corneal button was crystal clear, and the corneal thickness was normal at 0·56 mm. The lens was clear, the fundus was normal, and the patient was otherwise asymptomatic and on no medication.

CASE 3

The patient, a man then aged 24 years, was seen for repeat keratoplasty on his right eye on 26 September 1974. Two years earlier he had undergone thermokeratoplasty, followed by 2 successive penetrating keratoplasties, each of which has succumbed to a homograft reaction. On 26 September 1974 he underwent a 7·5 mm penetrating keratoplasty with continuous 10-0 monofilament nylon suture, with insertion of a tissue-typed donor cornea preserved in TC-199 medium. The vision at the time of discharge from the hospital was 6/18 (20/60). On 31 December 1974, about 3 months postoperatively, he was struck in the right eye accidentally with a champagne cork. He was seen by a physician in Florida, who noted that the graft wound had dehisced. On 2 January, 2 days after the injury, he arrived at the Wilmer Institute with a visual acuity of light perception. The anterior chamber was flat superiorly but formed inferiorly. Iris tissue and a considerable amount of fibrin were present in the wound superiorly (Fig. 2) and the graft had dehisced from 8 o'clock to 4 o'clock. There were old keratic precipitates on the posteroinferior surface of the graft. The patient was treated with high-dose systemic antibiotics (penicillin G and nafcillin) intravenously. In the operating room the iris was peeled from the posterior corneal surface. The lens had been subluxed posteriorly and was not retrieved. An anterior vitrectomy was performed. The corneal wound margins were surgically apposed and were sutured with multiple interrupted 10-0 monofilament nylon sutures. Postoperatively the graft cleared, and in December 1979, 5 years after the injury the visual acuity was 6/6 (20/20) with correction.

CASE 4

In August 1975, at age 30, this black male was admitted to the Wilmer Institute for penetrating keratoplasty in the left eye. Preoperatively 45 dioptres of left exotropia and high myopia with lattice degeneration of the retina with holes but no detachment in both eyes were noted. He had had thermokeratoplasty in March 1975 for keratoconus. The 7·5 mm penetrating keratoplasty with a running 10-0 monofilament nylon

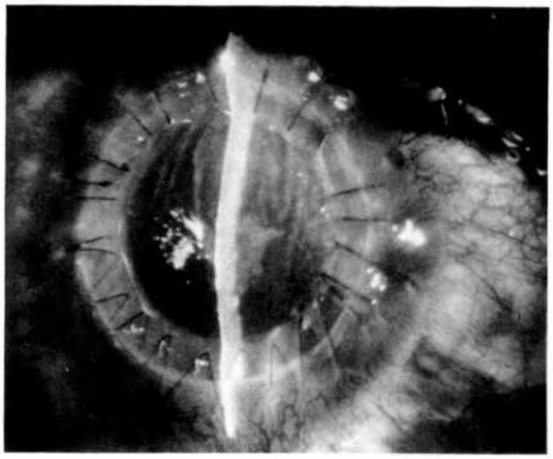

Fig. 3 *Two weeks after resuture of traumatic wound dehiscence the original graft remains quite oedematous. Interrupted sutures have reapproximated the tissue from 8 o'clock to 4 o'clock. Other interrupted sutures are tied to the ends of the broken running suture inferiorly, and the knots are buried (case 4).*

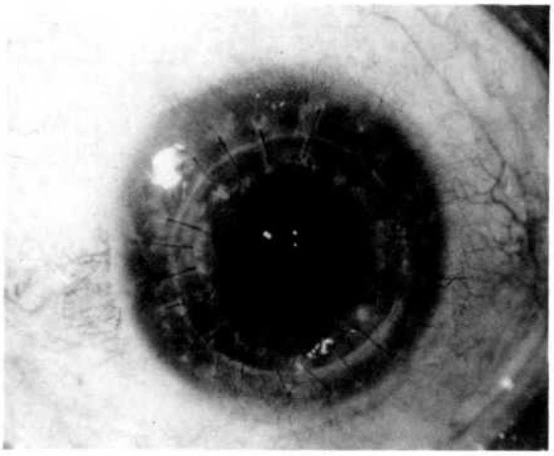

Fig. 4 *Six months after wound repair the original corneal button is clear (case 4).*

suture underwent an uncomplicated postoperative course such that at 5 weeks the visual acuity with pinhole was 6/12 (20/40). On 24 October, 8 weeks after keratoplasty, the patient was accidentally struck in the operated eye by his 3-year-old daughter's finger. He noted pain, blurred vision, and a wet sensation on his left cheek. At the Wilmer Institute in the emergency room the keratoplasty wound was found to have dehisced superiorly and the corneal button protruded between the eyelids, hinged by the remaining inferior sutures. At that time the lids were gently opened, the graft was repositioned, and the lids were taped closed. At surgery soon thereafter the lens was found to be absent, and the vitreous had prolapsed through the corneal wound. A generous anterior vitrectomy was performed, and the graft was resutured in place with interrupted 10-0 monofilament nylon suture. The loose ends of the running suture inferiorly were tightened and tied to interrupted sutures, and all knots were buried in cornea. In the early postoperative period the graft was thick and oedematous (Fig. 3), but it gradually cleared (Fig. 4), yielding a visual acuity of 6/15 (20/50).

Three months after the graft was resutured the patient was in a motor accident, immediately after which he noted a 'curtain' over the visual field of the left eye. A retinal detachment was found, and the repair required 2 operative procedures. A macular pucker ensued, reducing the visual acuity to a 6/60 (20/200) level with correction. However, the graft itself has remained crystal clear. In September 1978, 3 years after injury, a spontaneous peeling of the preretinal membrane was observed, and the visual acuity became 6/31 (20/70). The graft remains clear.

Discussion

All 4 patients were young males who had had penetrating keratoplasty for keratoconus (Table 1). Keratoconus is a common indication for penetrating keratoplasty,[6] and keratoconus is common among younger persons. Moreover young males as a group are the most prone to ocular injury.[7] Thus, although 4 other traumatic postkeratoplasty dehiscences have been reported in young males with keratoconus,[4,5] we believe it is the exposure of younger persons to the

Table 1 *Details of patients*

Case	*Age*	*Sex*	*Sutures present at injury*	*Interval (months) keratoplasty to dehiscence*	*Lens*	*Follow-up (months)*	*Visual outcome*
1	20	M	Interrupted	2½	Clear	23	20/30+1
2	24	M	Running	3½	In vitreous	59	20/20
3	30	M	Removed	72	Lost	29	20/20
4	30	M	Running	2½	Lost	35	20/70*

*Macular pucker following 2 scleral buckling procedures.

risk of trauma rather than any basic defect of wound healing in keratoconus that accounts for the prevalence of wound dehiscence in this group.

None of our patients was wearing protective wear. One patient received a blow to the eye during a bar-room brawl, one was struck by a Frisbee ricochet, one was struck by a champagne cork at a party, and one was accidentally poked in the operated eye by his 3-year-old daughter's finger during play. The force of the trauma was great enough to expel the lens through the wound dehiscence in 2 cases, the lens was dislocated and fell posteriorly in one case, while the lens remained in place in only one. In Raber *et al.*'s series[5] the lens was lost at the time of injury or surgical repair in 6 of their 7 phakic patients.

In 3 patients the injuries occurred rather soon after surgery: 2 of the injuries occurred at 2½ months and another was at 3½ months after operation. In each of these cases the operated eyes were receiving topical corticosteroids. The 10-0 monofilament nylon sutures were still present. In 2 cases the running sutures broke and the wounds were dehiscent superiorly, whereas in case 2 with interrupted sutures the inferior sutures broke. Our case 4 was a man who had received keratoplasty 5 years before. He had severe trauma to the eye, resulting in inferior rupture of the keratoplasty wound. While our cases showed equal representation of superior and inferior dehiscences, 10 of Raber *et al*'s 12 cases[5] suffered superior wound rupture, and 10 had nylon sutures still in place. The case described by Polack and Binder[4] occurred one week after suture removal at 3½ months after keratoplasty.

Gassett and Dohlman[8] have shown in the rabbit that by about 3 months after keratoplasty the tensile strength of a keratoplasty wound is only 50% of that of the normal intact tissue. Thus it is not at all surprising that ocular injury to a patient at 3½ months should result in dehiscence in the keratoplasty wound rather than rupture of the globe elsewhere. Our case of late wound dehiscence is similar to those reported by Friedman,[3] both occurring 4 and 5 years after keratoplasty. In each case the severe ocular trauma resulted in dehiscence of the keratoplasty wound, which suggests that surgical corneal wounds may never achieve the strength of normal cornea. The use of topical corticosteroids undoubtedly contributes to the prolonged weakness of corneal incisions.

In each of these cases the patient received primary resuturing of his corneal graft after the trauma. This was done despite the fact that all of these grafts appeared oedematous and opaque. Nevertheless the grafts went on to deturgesce slowly and to regain excellent clarity. With follow-up varying from 23 months to 5 years the grafts all remained clear. The visual acuity is excellent in 3 cases, 2 having 6/6 (20/20) vision and one having 6/9 (20/30) vision. The fourth has 6/21 (20/70) acuity because of macular pucker after 2 scleral buckling procedures for traumatic retinal detachment. In Raber *et al.*'s series[5] the final visual acuity was better than 6/60 (20/200) in only 4 patients. Regrafts were carried out at some time after injury in 4 eyes, and one other patient was awaiting regraft.

On the basis of these experiences we suggest the following approach. Under general anaesthesia the original graft should be repositioned and resutured in the recipient bed with interrupted 10-0 monofilament nylon suture as soon as possible. If the patient has been rendered aphakic by the injury, a Flieringa ring should be sutured to the globe to give support, and then an anterior vitrectomy should be performed. Cultures should be taken and the patients treated with prophylactic antibiotics. Postoperatively the physician should exercise patience in waiting for the graft to clear. We also suggest the use of safety glasses by all young patients after penetrating keratoplasty in the hope of preventing these severe (and sometimes disastrous) ocular injuries.

Endothelial cell loss occurs after intraocular surgery.[9] Presumably the amount of cell loss parallels the degree of endothelial trauma that occurs intraoperatively. Most corneal surgeons have the impression that almost any touch of the corneal endothelium at the time of grafting will result in corneal oedema. One would assume that an injury serious enough to cause postoperative wound dehiscence, expulsion of the lens, and loss of vitreous through the wound opening (thus resulting in vitreal-endothelial touch and a temporarily flat anterior chamber) would also cause considerable endothelial trauma. In our cases, however, the graft endothelium apparently had enough functional reserve to withstand the blow to the eye; and despite the immediate post-traumatic oedema, corneal function improved after repair of the dehiscence so as to restore graft clarity in each case. Therefore some physiological change must occur in the donor endothelium after it has adapted to the recipient eye for several months to allow it to withstand such severe insults as occur with traumatic wound dehiscence, while much milder trauma at initial transplantation surgery may result in permanent corneal oedema. It is of interest that the case of graft failure reported after traumatic wound dehiscence that was studied by Polack and Binder[4] showed absence of Descemet's membrane and the endothelium over half of the graft specimen, which indicates why the graft failed to clear.

This work was supported in part by NIH academic investigator award EY-00156, Research to Prevent Blindness James L. Adams award, and Fight for Sight, Inc. grant in aid (Dr. Kenyon).

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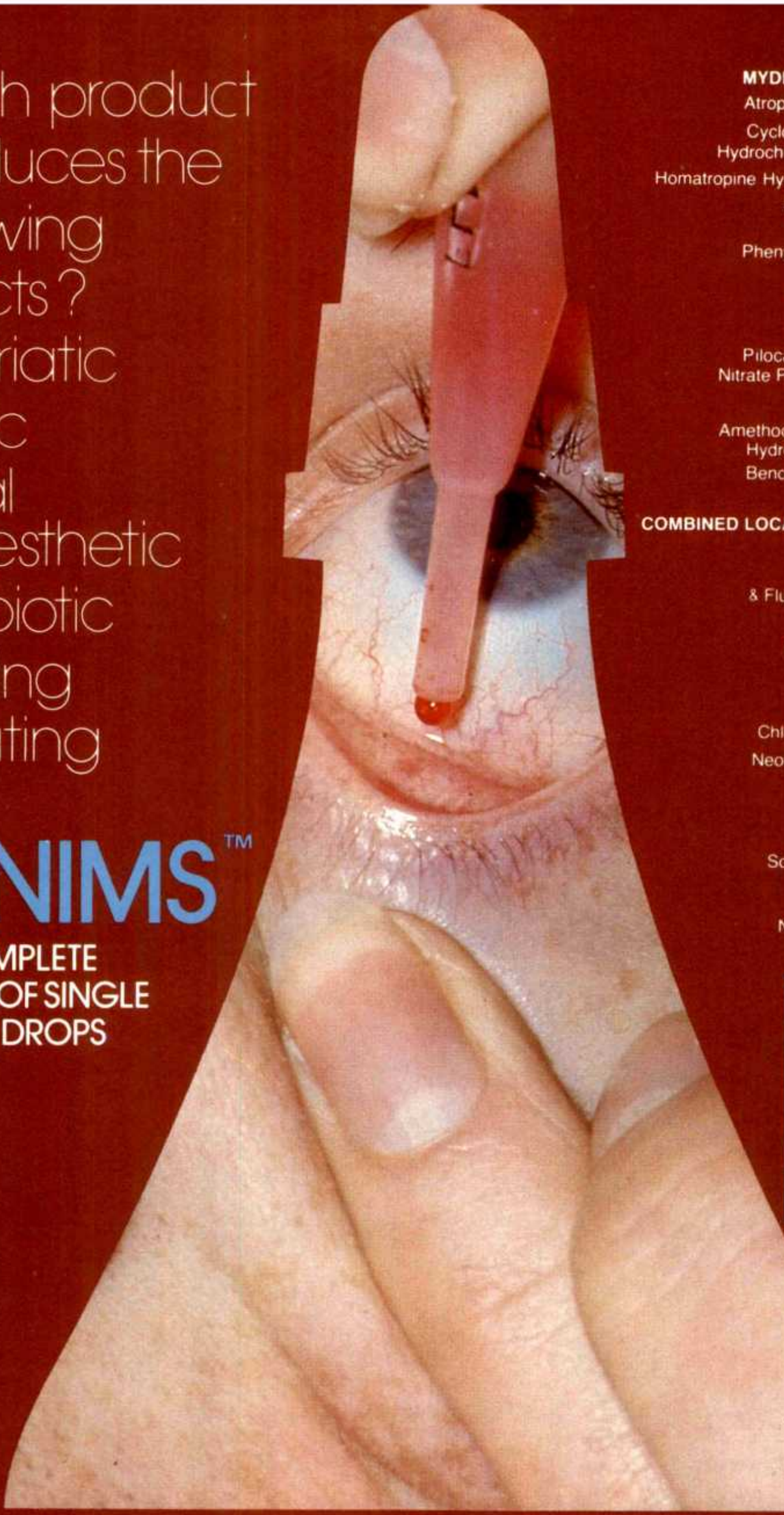

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British Journal of Ophthalmology, 1982, **66,** 179–182

Sterile corneal perforation after cataract surgery in Sjögren's syndrome

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SUMMARY Painless, sterile, noninfiltrated corneal ulceration and perforation, which may occur after recent cataract surgery in patients with rheumatoid arthritis and Sjögren's syndrome, appears to be a distinct clinical entity. The cause is probably multifactorial. Contributing factors may be the underlying systemic disease process in rheumatoid arthritis and Sjögren's syndrome, the associated keratoconjunctivitis sicca, the surgical procedure, and the postoperative use of oral and topical corticosteroids. Two cases of this clinical entity are reported here. Preoperative recognition by cataract surgeons that corneas in patients with rheumatoid arthritis and Sjögren's syndrome have an increased risk for postoperative ulceration should prompt postoperative preventive measures.

Sterile corneal thinning, ulceration, and perforation in patients with rheumatoid arthritis is a well-defined entity.[1–7] These documented corneal abnormalities have not been associated with ocular surgery. I am aware of only one reported case of central, sterile corneal perforation after recent routine cataract surgery in a patient with rheumatoid arthritis and Sjögren's syndrome.[8] I am reporting 2 additional patients to support my contention that postsurgical, painless, central, noninfiltrated, and sterile corneal ulceration and perforation in such patients is an important clinical entity worthy of definition. The multiple contributing factors which lead to this condition will be evaluated and recommendations offered for postoperative preventive measures.

Case reports

CASE 1

A 71-year-old white female with a history of severe rheumatoid arthritis since 1958 has been followed up by her ophthalmologist since 1966 for keratoconjunctivitis sicca, progressive cataracts, and bilateral senile macular degeneration. Therapy has been multiple artificial tear preparations. A diagnosis of Felty's syndrome was made in 1978, and treatment with oral prednisone was started. A splenectomy was performed on 31 October 1979.

In July 1979 the best corrected visual acuity was 6/15 in the right eye and 6/24 in the left eye. There were hyperaemia and crusting of all lid margins. Biomicroscopic examination showed punctate epithelial erosions of the inferior one-third of each cornea, and both lenses showed moderate nuclear sclerosis. A Schirmer I test showed 1 mm of wetting in 5 minutes in each eye. Goldmann applanation intraocular pressures were 10 mm Hg in each eye. In September 1979 visual acuity had decreased to 6/30 in each eye because of progressive lenticular nuclear sclerosis.

On 31 March 1980 the patient was treated with oral acetazolamide and topical 2% pilocarpine hydrochloride for an attack of acute angle-closure glaucoma in the right eye. On 1 April 1980 the intraocular pressure was normal and the acetazolamide was stopped. Progression of the right cataract decreased the visual acuity to 6/60.

On 3 May 1980 the patient had another attack of acute angle-closure glaucoma in the right eye and was immediately admitted to hospital. Treatment with intravenous 20% mannitol was begun, and the glaucoma subsided within 12 hours. On 6 May 1980 an uncomplicated right intracapsular cataract extraction and a sector iridectomy were performed.

Postoperative treatment was atropine sulphate 1% ophthalmic solution every other day and Maxitrol (neomycin sulphate, polymyxin B sulphate, and dexamethasone) ophthalmic ointment twice a day. Artificial tear drops were also continued. The intraocular pressure remained normal, and at a post-

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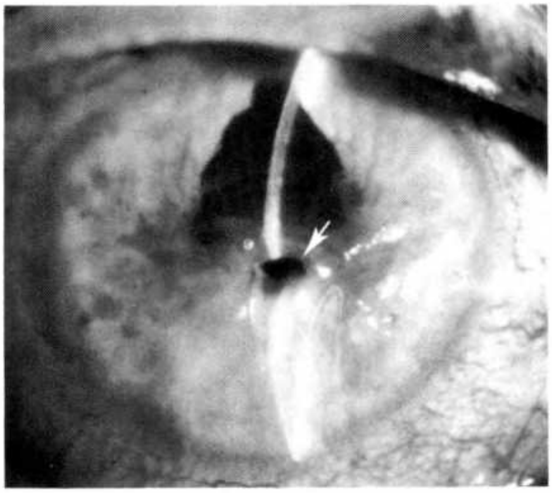

Fig. 1 *The right cornea had a sterile paracentral perforation (arrow) through which the vitreous had prolapsed.*

operative examination on 15 May 1980 the right cornea was normal. At the next routinely scheduled postoperative examination, on 28 May 1980, a painless, inferior, paracentral, right corneal perforation was observed. The patient was immediately referred to the Ophthalmology Clinic at North Carolina Memorial Hospital, Chapel Hill, North Carolina.

On admission the oral medication included 650 mg of aspirin 3 times daily, 5 mg of prednisone daily, and 25 mg of indomethacin 3 times daily. The visual acuity in the right eye with a +10·00 spherical lens was counting fingers at 2 feet (60 cm) and in the left eye was correctable to 6/30. Biomicroscopic examination of both eyes showed absent tear menisci. The right cornea had a slightly inferior paracentral perforation 1·5 mm in diameter without any surrounding infiltrate (Fig. 1). The vitreous had prolapsed through the perforation, the anterior chamber was shallow, and the eye was soft. There were punctate epithelial erosions of the inferior one-third of the left cornea. The peripheral anterior chamber was narrow, and the lens showed moderate nuclear sclerosis. Goldman applanation intraocular pressure in the left eye was 15 mm hg. Indirect ophthalmoscopy revealed only hazy details of the right optic nerve, macula, and retinal vessels. A normal optic disc, peripapillary retinal atrophy, and pigmentary dispersion in the macula were seen in the left eye.

On 29 May 1980 a corneal patch graft with isobutylcyanoacrylate tissue adhesive and a closed eye, and partial anterior vitrectomy with the Ocutome instrument in the right eye, were successfully performed. Corneal scrapings performed at the time of surgery for anaerobic and aerobic bacterial and fungal cultures resulted in no growth.

CASE 2

A 74-year-old white female with a 15-year history of severe rheumatoid arthritis has been followed up by her ophthalmologist for recurrent keratoconjunctivitis and progressive cataracts since 1972. When she was first examined the best corrected visual acuity was 6/6 in the right eye and 6/7·5 in the left eye.

In September 1979, because of a complaint of decreased vision, the patient was examined. The best corrected visual acuity in the right eye was 6/30 and in the left eye was 6/15. Both lenses were cataractous and accounted for the decreased visual acuities. A Schirmer I test measured 3 mm of wetting in 5 minutes in each eye. Goldmann applanation intraocular pressures were 12 mmHg in the right eye and 14 mmHg in the left eye. A diagnosis of keratoconjunctivitis sicca was made, and treatment with frequent Hypotears (artificial tears) drops was begun.

In June 1980 the best corrected visual acuity was again 6/30 in the right eye and 6/15 in the left eye. The patient was advised to have cataract surgery, and on July 31 1980 an uncomplicated, right intracapsular cataract extraction and a peripheral iridectomy were performed.

Postoperative treatment was atropine sulphate 1% ophthalmic solution daily and Maxitrol ophthalmic solution 3 times daily. The Hypotears drops were continued. Examination on 12 September 1980 showed no thinning or ulceration of the right cornea. At the next routinely scheduled postoperative examination on 29 September 1980 a painless, inferior, paracentral, right corneal perforation was observed. The patient was immediately referred to the Ophthalmology Clinic at North Carolina Memorial Hospital, Chapel Hill, North Carolina.

On admission the oral medications included 650 g of aspirin daily.

The visual acuity in the right eye with a +10·00 spherical lens was 6/120 and in the left eye was correctable to 6/30. Biomicroscopic examination of both eyes showed absent tear menisci. The right cornea had a slightly inferior paracentral perforation 1 mm in diameter. There was a small area of surrounding stromal oedema without any infiltrate, and the vitreous had prolapsed through the perforation. The anterior chamber was deep, and the eye was soft. There were punctate epithelial erosions and filaments of the inferior one-third on the left cornea, the anterior chamber was of normal depth, and the lens showed moderate nuclear sclerosis. Goldmann applanation intraocular pressure in the left eye was 15 mmHg. Indirect ophthalmoscopy of each eye revealed a clear vitreous, normal optic nerves, peripapillary retinal atrophy, and pigmentary dispersion in the maculae.

On 30 September 1980 a corneal patchgraft with isobutylcyanoacrylate tissue adhesive and a closed eye, and partial anterior vitrectomy with the Ocutome instrument in the right eye, were successfully performed. Corneal scrapings performed at the time of surgery for anaerobic and aerobic bacterial and fungal cultures resulted in no growth.

Discussion

The clinical entity of sterile, noninfiltrated, central and peripheral corneal thinning, ulceration, and perforation in patients with rheumatoid arthritis who have not undergone ocular surgery has been well defined.[1–7] Keratoconjunctivitis sicca or an alteration of the tear constituents has been suggested as one possible cause.[2 6 7] However, keratoconjunctivitis sicca does not appear to be a necessary requirement to produce these corneal changes, since corneal thinning, ulceration, and perforation have been seen in patients with rheumatoid arthritis and no keratoconjunctivitis sicca.[2] Furthermore, Krachmer and Liabson did not see corneal perforations in patients who had only keratoconjunctivitis sicca.[7] It may be postulated that the systemic immunological and pathophysiological abnormalities associated with rheumatoid arthritis sometimes cause sterile corneal ulceration in these patients.[9]

The relationship of topical and/or corticosteroids to the corneal ulceration which can occur in patients with rheumatoid arthritis is an unclear but important issue. There has been a frequent but not invariable association between topical corticosteroid therapy and corneal ulceration. In the largest reported series evaluating the treatment of corneal ulceration and perforation in patients with rheumatoid arthritis and Sjögren's syndrome, Pfister and Murphey reported that 9 of 18 eyes had received topical corticosteroids prior to the development of the ulceration or perforation.[8] Another study of patients with rheumatoid arthritis described 3 patients who developed corneal ulcerations after a topical corticosteroid was begun and one patient who developed a central corneal perforation while being treated with an oral corticosteroid.[2] Topical corticosteroids are thought to suppress the reparative corneal wound healing process by reducing new corneal collagen synthesis.[10] Thus, if associated keratoconjunctivitis sicca and/or the systemic immunological and pathophysiological abnormalities found in patients with rheumatoid arthritis initiate corneal ulceration, the use of topical and/or oral corticosteroids may potentiate this existing ulceration and result in corneal perforation.

The systemic pathophysiology of rheumatoid arthritis, the frequently associated keratoconjunctivitis sicca, and the use of topical and/or oral corticosteroids all increase the risk of sterile, corneal ulceration and perforation in patients with rheumatoid arthritis. Cataract surgery may provide several additional risk factors for the occurrence of these severe corneal complications in patients with rheumatoid arthritis. These risk factors are important to the cataract surgeon.

Sterile corneal ulceration and perforation after recent cataract surgery in patients with rheumatoid arthritis and Sjögren's syndrome does appear to be a distinct clinical entity. In the patient previously reported by Pfister and Murphey, who developed postoperative corneal ulceration and perforation, the site of involvement was the inferior, paracentral cornea, and the perforation occurred 6 weeks after surgery.[8] There are several important similarities between this patient and the 2 patients reported in this paper. All 3 patients (1) had corneal perforations within 3 to 8 weeks after cataract surgery, (2) used postoperative topical corticosteroids, (3) had noninfiltrated corneas, (4) had perforations located in the inferior, paracentral cornea, and (5) had sterile corneal cultures for bacteria and fungi.

It should also be noted that these postoperative corneal perforations are painless and can occur without warning. The 2 patients reported in this paper had no postoperative corneal abnormalities noted at the preceding examinations (9 and 43 days after surgery respectively) prior to the perforation. At the next routinely scheduled examinations, 11 and 17 days later respectively, the corneal perforations were noted.

There are several potential postoperative risk factors that may promote and/or potentiate these painless, noninfiltrated, central corneal ulcerations. It may be postulated that surgery can aggravate the underlying systemic pathophysiological process associated with rheumatoid arthritis, which can then cause these corneas to ulcerate. Bloomfield *et al.* suggested that systemic vasculitis may be a possible cause of corneal abnormalities after cataract surgery.[11] They reported a patient with a diffuse vasculitis who developed painful, infiltrated, sterile, peripheral corneal ulcerations after cataract surgery. Immunopathological studies demonstrated immunoglobulins and complement in the walls of the conjunctival blood vessels. These corneal changes were similar to previously reported marginal corneal ulcerations after recent cataract surgery, and one of these patients had a positive serum latex test.[12 13] Patients with rheumatoid arthritis can have a vasculitis.[9] Bloomfield *et al.* further suggested that because patients with rheumatoid arthritis can have circulating immunocomplexes they may be at special risk for scleral and corneal melting after cataract surgery. Although the clinical description of Bloomfield *et al.*'s patient is different from Pfister and Murphey's patient and the 2 patients in this report, the underlying pathophysiology for corneal ulcerations in these patients with rheumatoid arthritis may be similar.

Another postoperative risk factor appears to be topical corticosteroids which are routinely administered after cataract surgery. One of the patients reported in this paper was receiving not only a postoperative topical corticosteroid but also an oral corticosteroid for the treatment of her arthritis. In the past she also received an oral corticosteroid for the treatment of Felty's syndrome. Patients with rheumatoid arthritis are frequently receiving oral corticosteroids for the treatment of arthritis and disease-associated medical complications.

The effects of keratitis sicca may be potentiated postoperatively, since surgery may interfere with lid mobility, and postoperative corneal denervation may reduce blinking. Radtke *et al.* reported 5 patients with only preoperative keratoconjunctivitis sicca who had sterile, noninfiltrated, paracentral corneal ulceration after cataract surgery.[14]

Patients with rheumatoid arthritis and Sjögren's syndrome have corneas which can ulcerate and perforate without the added stress of cataract surgery. The recognition by cataract surgeons that the corneas of these patients have added risks for postoperative sterile ulceration and perforation should prompt preventive measures. The routine postoperative administration of topical and oral corticosteroids should be minimised or avoided, and intensive treatment of keratitis sicca should be instituted. Complete blinking can be encouraged, and incomplete lid closure should be corrected.

This study was supported by an unrestricted grant from Research to Prevent Blindness Inc.

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We regret the poor quality of the paper used for pages numbered 183–204 in the March issue. These pages are issued as replacement.

British Journal of Ophthalmology, 1982, **66**, 183–185

Extracapsular cataract extraction—some problems

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SUMMARY Comments are made on the method of removing the anterior capsule during the performance of extracapsular cataract operations. The difficulty of performing this manoeuvre adequately is emphasised. Observations carried out during the postoperative period by means of the slit-lamp revealed some hitherto undescribed changes in the capsule. The edge of the anterior capsule can be clearly seen and looks like broken glass. Fine fibrils have been observed attached to the fractured capsular edge. In the early postoperative period the anterior capsule tends to be separated from the posterior by quite a deep space, but at an early stage, usually about the fourth day, the edge of the anterior capsule becomes adherent to the posterior capsule, and rather rapidly a dense fibrous line forms along the joint.

We have been through a period in ophthalmology in the 1950s and 1960s when extracapsular cataract extraction had practically ceased—so much so that there is now a whole generation of ophthalmologists who have hardly been taught how to express a nucleus. Extracapsular cataract extraction is a very old operation, the first description being by Jaques Daviel in 1753.[1] The after-cataract which tends to form in the scaffolding of the remnants of capsule and lens matter has been extensively studied by Soemmering[2] and many others. Duke-Elder[3] stated that in Soemmering's ring the edges of the anterior capsule adhere to the posterior but that fibrous cells may be laid down on the posterior capsule by fibroblasts from the iris. Furthermore, the subcapsular epithelium comes to line the ring—both anterior and posterior capsules. Bladder cells, Elschnig's pearls,[4] and their possible removal by irrigation are also mentioned.

The indications for extracapsular surgery are present in any case of cataract where for some reason intracapsular extraction is thought to be hazardous or unsuitable. Absolute indications would be when the patient is below the age of 40 years, where later surgery is contemplated, or where irido-drainage surgery is contemplated, or where irido-capsular pseudophakos is planned. Relative indications would be patients between the ages of 40 and 60, patients with high myopia, and patients in whom ischaemic retinopathy is suspected.

Material and methods

The eyes of patients undergoing routine extracapsular cataract surgery at the Western Ophthalmic Hospital were observed during the year 1980. Particular attention was given to the slit-lamp appearances in the early postoperative period, and photographs were taken of the anterior capsule where appropriate on the second, fourth, and several subsequent days. In addition some photographs were taken during the course of extracapsular surgery in the operating theatre.

The surgical technique consisted in the forming of a limbal groove ab externo, the insertion of 3 preplaced sutures, and puncture of the anterior capsule with a hooked blue disposable needle attached to a drip of Hartmann's solution. The section was then opened and removal of the anterior capsule carried out, usually with Arruga's capsule forceps.

We tried to ensure that the removal of the anterior capsule should be as complete as possible, because while removing anterior capsule one is probably also removing active subcapsular epithelium and minimising the chance of after-cataract. (There have been recent pronouncements on the subjects of anterior capsular removal following the upsurge of interest consequent on phakoemulsification and pseudophakos. For example, Arnott[5] recommended cutting the capsule in the shape of an inverted Christmas tree, the 'tree' being drawn out by fine toothed forceps, and Kelman[6] advised an approxi-

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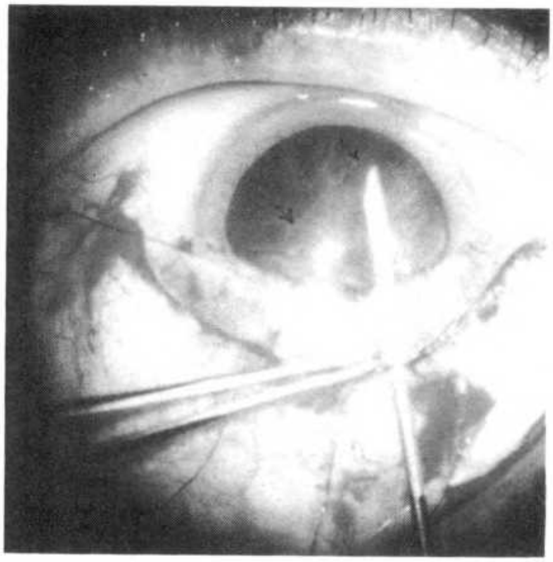

Fig. 1 *While the capsule is being cut with a hooked blue needle, it tends to split in a linear fashion. Arrows indicate edge of split capsule.*

mately similar manoeuvre carried out under an air bubble.)

After removal of capsule the nucleus was expressed and the wound temporarily closed by tying the sutures in bows. Irrigation-aspiration by a double cannula could then be carried out at leisure as in the closed technique, and at the conclusion of this procedure, or sometimes before it, a peripheral iridectomy was performed. Finally the bows were tied permanently or were undone and retied later if it was intended to insert an intraocular lenticulus.

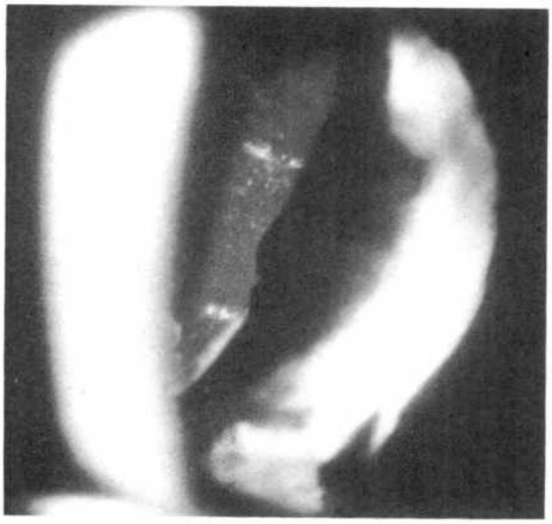

Fig. 2 *Broken-glass appearance of anterior capsule remnants 2 days postoperatively.*

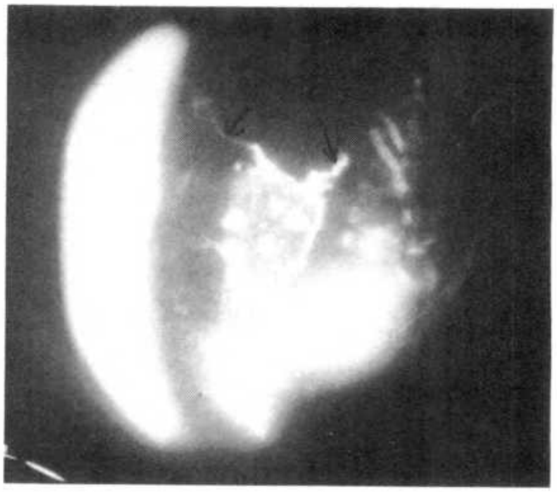

Fig. 3 *Fibres 'growing' from edge of cut capsule 2 days postoperatively. Normally the fibres are very fine; these appear to have an opaque coagulum on them making them more visible than usual.*

Results

We found that the anterior capsule tended to split in an erratic fashion, like tearing Cellophane, once it was pricked with a hooked blue needle—and the direction of the split was difficult to control. Furthermore, unless the microscope was zoomed up to a high magnification it was very difficult to see what was happening (Fig. 1). However, in many cases the capsule could be divided in a fairly satisfactory manner, hooked or rolled up towards the section, and eventually grasped with forceps, cut, and removed. It was important to include cutting in this procedure, since if pure traction was used it was possible to pull out the capsular rug from under the nucleus.

After lens extraction the edge of the anterior capsule could be seen in the anterior chamber looking very like broken glass (Fig. 2).

At an early stage—certainly within 3 days—fine fibrils appeared to be growing out of the fractured edge, though it was not clear whether they were only existing lens fibres whose position had been disrupted by the surgery (Fig. 3).

In 3 to 4 more days the anterior capsular edge moved backwards and became adherent to the posterior capsule. It was doubtful whether it was drawn backwards by contracture of the previously mentioned fibrils, which may first have become attached to the posterior capsule, or whether the

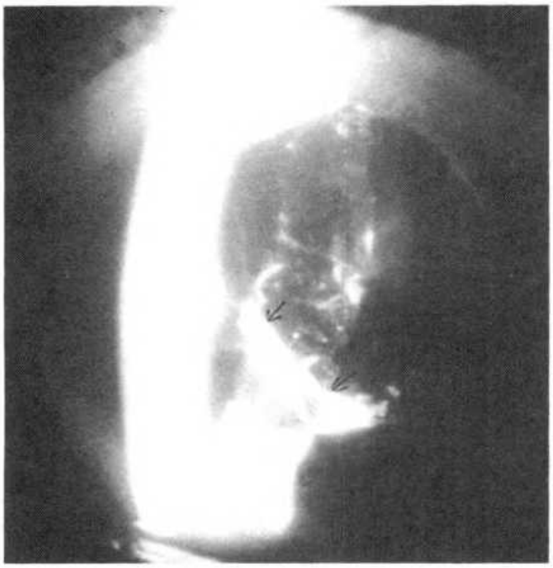

Fig. 4 *The anterior and posterior capsules rapidly unite: arrow indicates junction.*

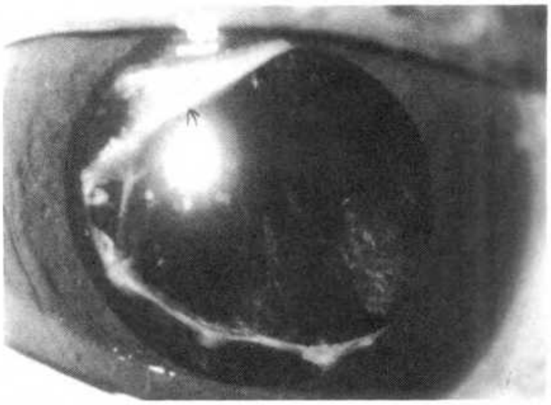

Fig. 5 *One year after extracapsular extraction (fellow eye of Fig. 4). The approximately annular line of junction between anterior and posterior capsules marked by dense fibrous tissue can be clearly seen.*

backward movement was a chance one resulting from swirling currents in the anterior chamber, the adhesion to the posterior capsule being possibly mediated by the fibrils (Fig. 4). After a little longer the line of junction between the edge of the anterior capsular remnant and the intact posterior capsule became marked by dense fibrous tissue. It seems likely that this tissue is the successor to the fine fibrils originally noted, so that the mechanism mentioned by Duke-Elder of fibroblasts originating from the iris is probably incorrect. A question which interests us is why lens cells sometimes form dense fibrous bands and at other times the clear bladder cells with which we are familiar. The fibrous bands tend to form preferentially at the broken edge of the anterior capsule where it becomes tied down to the posterior capsule (Fig. 5).

Discussion

The main point of this paper is to draw attention to the hitherto undescribed changes in the position of the anterior lens capsule immediately following surgery and also to mention the fine fibrils sometimes found on the capsular edge. It is uncertain whether these changes will prove to have any particular clinical or histopathological significance, but further extended observations on the behaviour of the anterior capsule may possibly yield some more interesting information.

We should like to emphasise in conclusion that we believe removal of the anterior lens capsule over as extensive an area as possible is the key to success in cataract surgery and that manoeuvres such as polishing the posterior capsule and even the exceptionally careful and complete removal of cortical material are of less importance than the removal of anterior capsule as efficiently as possible.

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British Journal of Ophthalmology, 1982, **66**, 186–189

Bilateral proptosis, dilatation of conjunctival veins, and papilloedema: a neuro-ophthalmological syndrome caused by arteriovenous malformation of the torcular Herophili

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SUMMARY A patient with an occipital dural arteriovenous malformation (AVM) developed signs of a carotid-cavernous sinus fistula and raised intracranial pressure. Bilateral transverse sinus occlusion associated with the AVM produced these signs by rerouting intracranial venous drainage anteriorly through the cavernous sinuses and superior ophthalmic veins. Angiography and computerised tomographic reformation techniques were used to define these extraordinary cranio-orbital venous pathways.

Orbital and ocular signs of a carotid-cavernous sinus fistula can be produced by any posteriorly located arteriovenous malformation (AVM) draining anteriorly into the orbital venous system.[1-9] Ocular signs of raised intracranial pressure (ICP) can be produced by any intracranial AVM that causes a rise of pressure in the posterior dural sinuses.[10]

We report major alterations in cerebral, dural, and orbital venous systems, confirmed by angiography and computerised tomography (CT), in a patient whose AVM at the torcular Herophili (confluence of superior sagittal, straight, and transverse sinuses) caused a clinical syndrome of bilateral proptosis, dilated conjunctival veins, and papilloedema.

Case report

This 25-year-old woman had a 4-year history of raised ICP that was caused by a dural AVM of the torcular Herophili. In August 1979 she noted proptosis of the

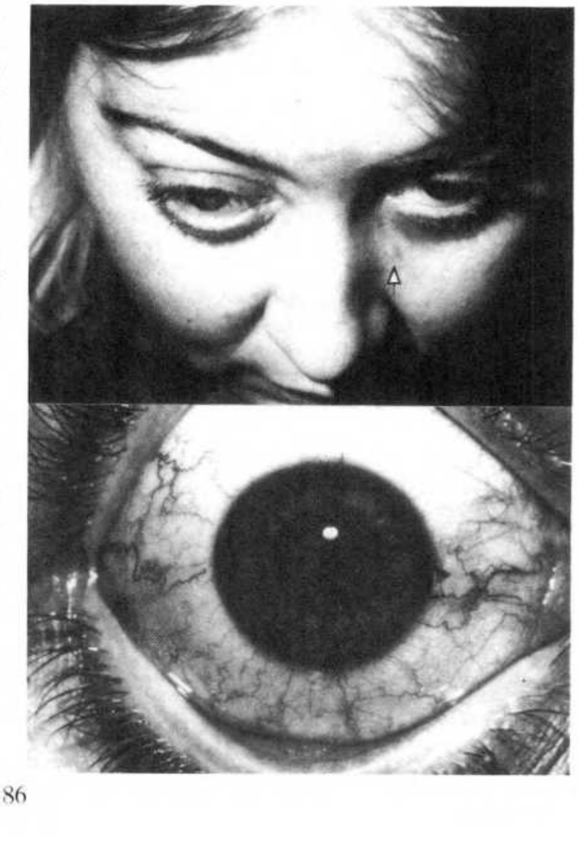

Fig. 1 Top: *Face photograph showing bilateral asymmetrical proptosis (exophthalmometer readings right 25 mm, left 22 mm) and enlarged left angular vein (arrow).* Bottom: *Right eye showing dilated conjunctival veins.*

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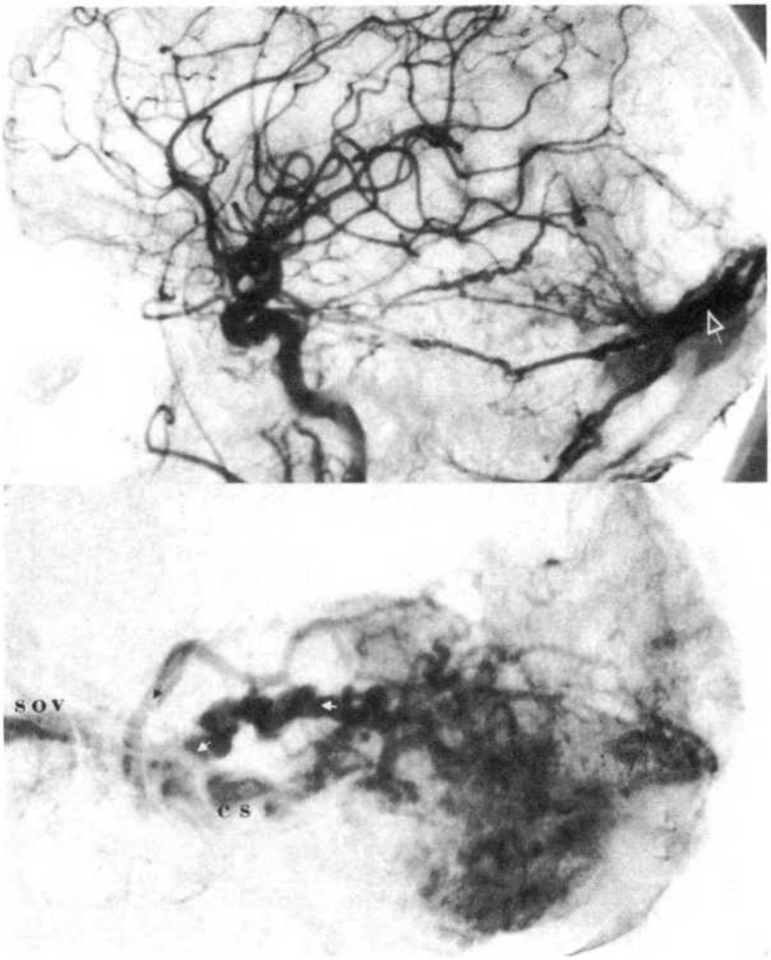

Fig. 2 Top: *Common carotid angiogram showing the torcular AVM (arrow), with feeder vessels from the occipital artery, posterior branches of the middle meningeal artery, and meningeal branches of the internal carotid artery.* Bottom: *Venous drainage of the malformation through the superficial middle cerebral vein (above), and deep cerebral veins (below), into the cavernous sinus (CS) and superior ophthalmic vein (SOV) (small arrows indicate direction of flow).*

right eye, redness of both eyes, and increasing headaches. Her visual acuity was 6/6 bilaterally, and she had asymmetrical proptosis that was bilateral, but more marked on the right (Fig. 1, top), dilated conjunctival vessels in both eyes (Fig. 1, bottom), and a prominent angular vein on the right. Intraocular pressures were normal. She had chronic papilloedema bilaterally and a partial homonymous hemianopia of the left visual field.

Selective carotid and vertebral angiography showed an occipital dural AVM with feeding vessels from the right and left occipital arteries, the posterior branches of the right and left meningeal arteries, and tentorial branches of the right and left internal carotid artieries (Fig. 2, top). Both transverse venous sinuses were totally occluded. Venous drainage from the AVM and from the brain flowed in a retrograde direction (Fig. 2, bottom) through: (1) the straight sinus, the vein of Galen, and deep cerebral veins; (2) the superior sagittal sinus and the superficial middle cerebral veins; (3) the meningeal veins.

These venous pathways and all others from within the skull entered the cavernous sinuses and the superior ophthalmic veins. The latter veins were markedly dilated (Fig. 3, top).

Axial CT scans showed portions of the occipital AVM, as well as the dilated basal veins and the anterior extensions of these veins toward the anterior cavernous sinuses.

By means of a research 'trace programme' (General Electrical Medical Systems, Milwaukee, Wisconsin, USA) vertical reformations along the wandering path of the dilated and contrast-enhanced veins in the basal cisterns permitted accurate identification of the point at which the enlarged basal veins penetrated the dura around the cavernous sinus, the superior orbital

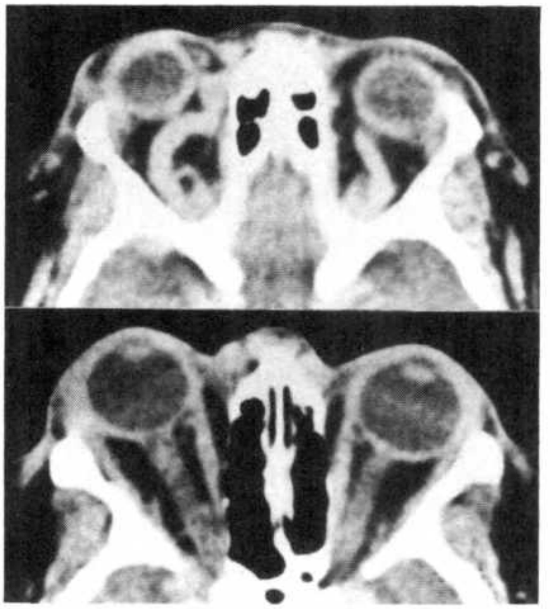

Fig. 3 Top: *Axial computerised tomography scan showing trace programme along a contrast-enhanced basal vein.* Bottom: *Lateral view of vertical reformation of same vein.*

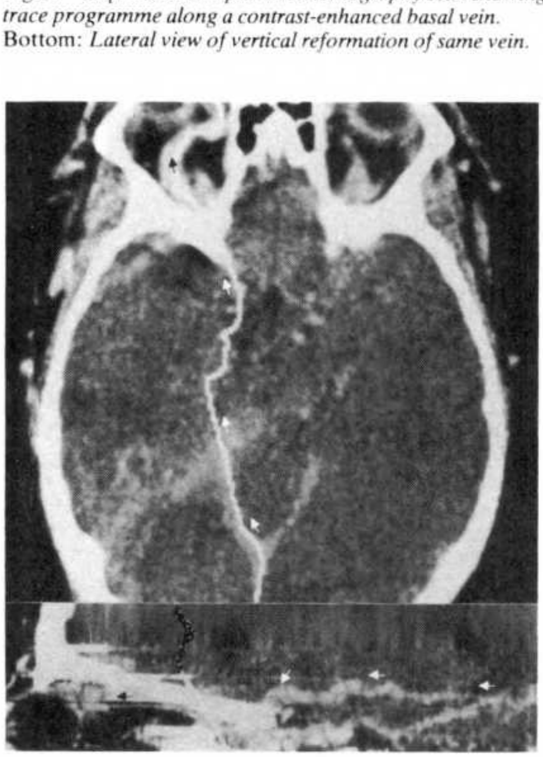

Fig. 4 Top: *Postcontrast axial computerised tomography scan showing markedly dilated superior ophthalmic veins.* Bottom: *Postcontrast axial scan indicating enlarged optic nerve sheaths.*

fissure, and entered the orbit (Fig. 4). In addition the CT scans of the orbit showed enlargement of the optic nerves secondary to dilatation of the vaginal sheath spaces (Fig. 3, bottom).

Radical resection of the dural AVM relieved the elevated pressure in the retrograde venous outflow channels at the base of the brain in the cavernous sinuses and in the orbital venous system. The patient's proptosis resolved, and the conjunctival redness and papilloedema disappeared.

Discussion

When posteriorly located dural AVMs cause bilateral transverse sinus occlusion,[11] a major rerouting of venous blood from the head must occur. Blood shunted through the AVM flows anteriorly in a retrograde direction through the basal, cortical, and dural veins toward the cavernous sinus. As exemplified by the CT and angiographic findings in the patient we describe, the basal veins become grotesquely enlarged, their calibre exceeding that of the carotid arteries. Before they pierce the dura of the anterior cavernous sinus they occupy a position first adjacent and just lateral to the optic nerves and chiasm, and then lateral and inferior to the anterior clinoid processes.

In the absence of adequate alternative venous outflow channels from the cavernous sinus, blood from the basal veins, together with blood from the sphenoparietal and cavernous sinuses, flows in a retrograde manner into the orbital venous bed. As a result orbital veins dilate, and the patient develops bilateral proptosis and dilated conjunctival vessels, thus simulating the features of a carotid-cavernous sinus fistula. These signs, together with evidence of raised ICP, including papilloedema, constitute an unusual neuro-ophthalmic syndrome suggesting a dural AVM with major sinus occlusion.

This study was supported in part by fellowship grants from the Royal College of Surgeons of England, Keeler Instruments, Ltd. (UK), and the Eastern Health and Social Services Board, Northern Ireland.

The authors thank Dr Michael Edwards for referring the patient to us, Susan Eastwood for excellent editorial assistance, and Beverly McGehee for preparation of the manuscript.

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British Journal of Ophthalmology, 1982, **66**, 190–193

Liposarcoma of the orbit: a clinicopathological case report

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SUMMARY Liposarcoma is a very rare primary tumour of the orbit. The present report describes changes seen by computed tomography, carotid angiography, and histopathology and gives a review of the literature.

Liposarcoma is an uncommon mesenchymal tumour. It shows a preference for certain locations such as the lower limbs and the retroperitoneal region.[1] In the orbit only a few cases of histopathologically verified liposarcomas have been reported. It is the object of this report to describe an additional case of primary liposarcoma of the orbit and to give a review of the literature.

Case report

In August 1977 the patient, a 58-year-old woman, was admitted to the University Eye Clinic in Uppsala with painless left-sided exophthalmos of almost one year's duration. Apart from 5 mm protrusion of the left eye she had no clinical abnormalities. Plain *x*-ray of the orbit was normal. Computed tomography (CT), however, revealed a tumour mass in the mediolateral part of the left orbit (Fig. 1). The attenuation in the tumour varied in different parts, with CT-numbers ranging from +5 to +15 Hounsfield units (HU). Following intravenous contrast injection (60 ml Isopaque Cerebral, Nyco, Oslo, Norway) there was a moderate increase in attenuation, with CT numbers between +20 and +30 HU. By carotid angiography the tumour was seen to be supplied by small branches from the ophthalmic artery, and the tumour displayed a marked blush in the venous phase (Fig. 2a, b). A fine-needle apiration biopsy contained regular endothelial cells of normal appearance, whereas pathological cell forms were lacking. At surgery a firm and lobulated tumour was easily removed by lateral orbitotomy. The postoperative period was uncomplicated. The patient has been followed up for 3½ years and she has not shown any clinical or CT signs of tumour recurrence.

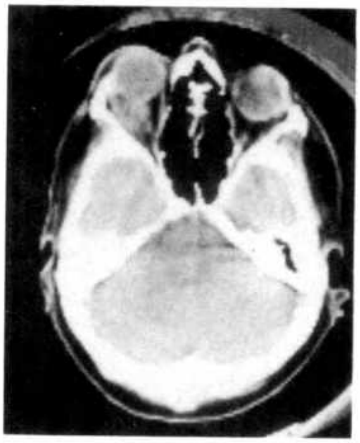

Fig. 1 *CT scan showing large retrobulbar tumour in the left orbit and marked exophthalmos.*

OPHTHALMIC PATHOLOGY

The tumour measured 33×27×27 mm. It had a firm consistency and a greyish to yellowish cut surface. Histologically the tumour showed both loose and solid areas. In the loose areas the predominant cell type was a rather small spindle to stellate cell with poorly defined boundaries. The nuclei were small and dense, giving an impression of pyknosis. The cells were loosely arranged in a slightly eosinophilic mucoid matrix (Fig. 3a) which stained weakly with alcian blue stain and colloid iron stain. It was weakly metachromatic with toluidine blue. After digestion with testicular hyaluronidase for 2 hours at 37°C

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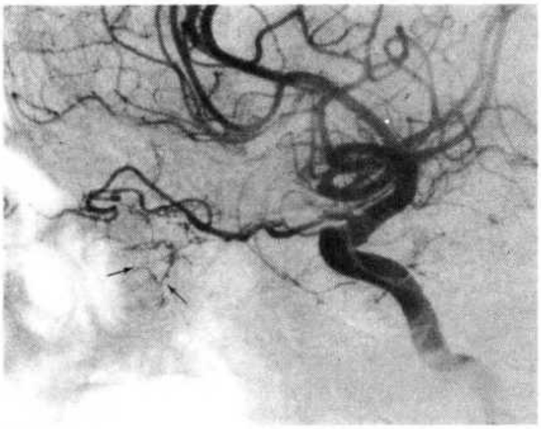

Fig. 2a

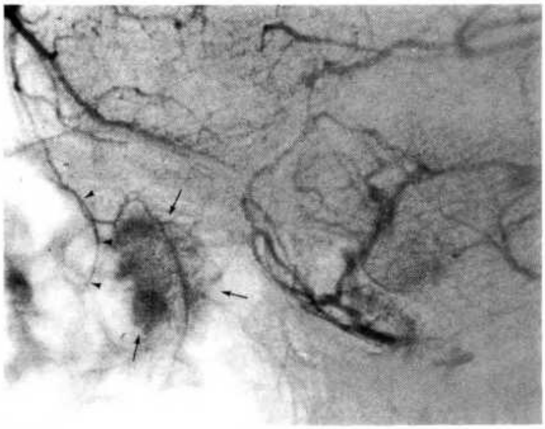

Fig. 2b

Fig. 2 *Internal carotid angiography.* (a) *The arterial phase shows delicate tumour vessels (arrows) from the ophthalmic artery.* (b) *The venous phase shows tumour blush (arrows). The position of the eye globe is seen by the contrast enhancement of the choroid (wedges).*

neither of the stain were positive, thus indicating that the background material consisted mainly of acid mucopolysaccharides. In the periphery of the mucoid areas there was a successive transition into areas with immature lipocytes (Fig. 3b). These cells showed more definite cytoplasmic borders and their cytoplasm contained coarse vacuoles. The round or oval nuclei showed obvious polymorphism and were placed either centrally or peripherally in the tumour cells. Mitosis or bizarre cell nuclei were not observed.

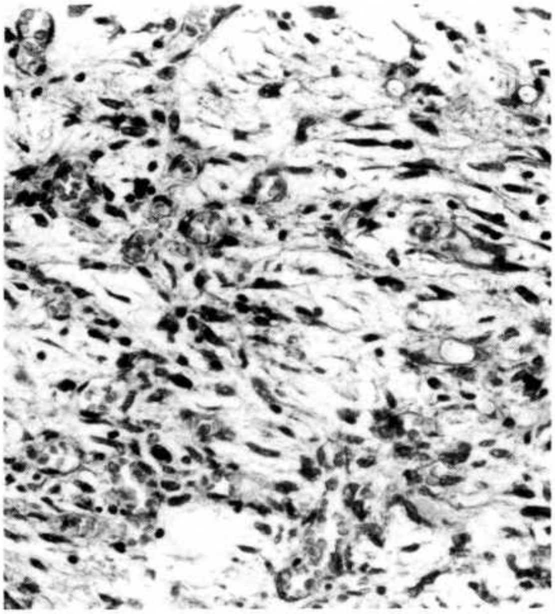

Fig. 3a

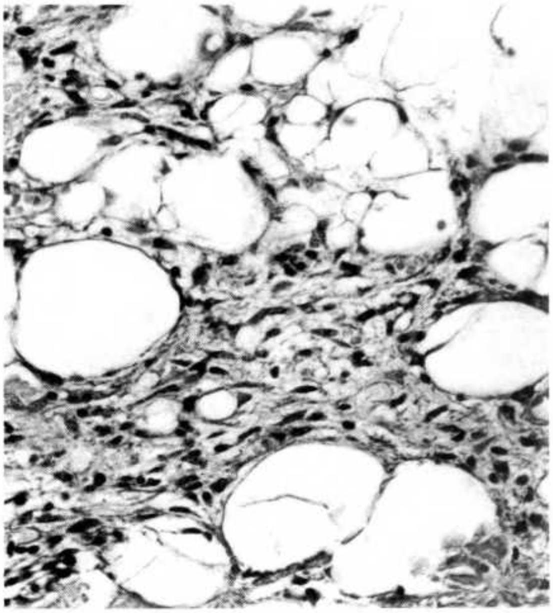

Fig. 3b

Fig. 3 (a) *Myxomatous area of the liposarcoma with stellate and spindle shaped cells. Note the maze of capillaries.* (b) *Part of the tumour showing lipocytes in different stages of maturation. (HE, ×240).*

In some areas there was a successive change of the cells into mature lipocytes. The solid areas were built up by fibrotic strands crossing through the tumour tissue. The lipocytes stained bright red with scarlet red and black with Sudan black. The lipid drops varied in size from very small to coarse in the immature cells, whereas only large drops filled the mature lipocytes. Throughout the whole tumour there was a rich capillary network. This was most prominent in the areas showing the lowest degree of cellular differentiation. Large vessels were rare. The tumour had a pseudocapsule of condensed tumour cells as its outer limit.

In accordance with the histopathological findings the tumour was diagnosed as a well differentiated myxoid liposarcoma of the orbit.

Discussion

Liposarcomas of the orbit are very rare tumours and to our knowledge only 11 cases have been reported.[2–11] Various authors[3 4 12 13] have classified these tumours. According to the classification by Enzinger *et al.*,[13] which was accepted as the WHO classification of 1969, 4 different types of liposarcomas may be separated, namely, myxoid, embryonal round cell, well differentiated, and pleomorphic. In the present case the histological diagnosis of myxoid liposarcoma was based on the presence of proliferating lipocytes in various stages of differentiation, the myxoid hyaluronidase-sensitive acid mucopolysaccharides, and the prominent capillary network. In the previously reported cases the myxoid type has been predominant.

The examination by CT revealed a retrobulbar tumour with mixed attenuation. The CT characteristics of this kind of tumour located in the orbit has not to our knowledge been described hitherto. The CT characteristics of liposarcoma in other regions such as extremities, mediastinum, and retroperitoneum have been reported.[14–16] In these cases there was a wide range in attenuation values of the tumours (from −90 to +30 HU), and in some cases with low attenuation values the fatty origin of the tumour could be predicted from the CT scan. However, the attenuation in the present tumour did not indicate the lipomatous character of the mass.

Carotid angiography showed a highly vascularised tumour. Several angiographic patterns of liposarcomas have been described,[17–20] but they did not differ from those seen in other malignant tumours.

Fine-needle aspiration has been shown to be of great help in diagnosing orbital tumours.[21] In the present case only endothelial cells were obtained and a definitive diagnosis could not be made. However, in view of the maze of capillaries in the tumour this finding is not surprising.

Radical surgery is generally regarded as the treatment of choice for liposarcoma. Jones and Jakobiec[11] described 2 cases of orbital liposarcoma which both primarily had no other therapy than surgery. In both these cases there were clinical signs of recurrence of the tumour one year later. In the case of liposarcoma reported by Schroeder *et al.*[10] 2 years passed before there were clinical signs of tumour recurrence. In these 3 cases radiation therapy was given after the recurring tumour had been removed by orbital exenteration. In the present case the patient has been followed up for 3½ years postoperatively and she has not shown any signs of tumour recurrence clinically or by CT. According to Schäfer and Wellens[19] radiation therapy should always be given to liposarcomas irrespective of the histological diagnosis. In cases of myxoid liposarcomas irradiation alone may be curative. Cytostatic drugs are recommended only in cases with metastases, where a rate of remission of 40% has been reported.[22]

In retrospect it seems that the prognosis of orbital liposarcomas is rather favourable and that the tumour may not recur after orbital exenteration combined with irradiation and finally chemotherapy.

The skilled technical assistance of Margareta Björling and Cristina Bittkowski is gratefully acknowledged.

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British Journal of Ophthalmology, 1982, **66**, 194–204

Primary orbital schwannomas

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SUMMARY Seven histologically proved cases of primary orbital schwannoma have been seen at the University of British Columbia Orbital Clinic between September 1976 and December 1980. We describe here their varied clinical presentations, preoperative investigations, operative findings, and appearances on light and electron microscopy. Although no single feature is pathognomonic, a multiplicity of clinical, radiographic, and surgical features point to this lesion. Of preoperative investigations the computed tomography scan was the most helpful, especially in localising the lesion. Of the 7, 4 were intraconal and 3 were extraconal. The surgical approach was dictated by tumour site and included anterior, lateral, and panoramic orbitotomies. At surgery the nerve of origin of 4 of the tumours was identified. All tumours were excised totally or subtotally. There has been no recurrence to date.

Schwannomas account for 1% of orbital tumours[1 2] and may arise anywhere within or adjacent to the orbit.[3] We have seen 7 histologically proved cases of schwannomas in the Orbital Clinic at the University of British Columbia between September 1976 and December 1980. We describe here their varied clinical presentations, preoperative investigations, operative findings, and appearances on light and electron microscopy.

Materials and methods

During the period from September 1976 to December 1980 484 cases were seen in the Orbital Clinic at the University of British Columbia, of which 123 represented mass lesions. Seven of these were found to be schwannomas, representing 1·4% of all orbital cases seen and 5·7% of mass lesions.

Diagnostic investigations included computed tomography (CT) scan (EMI 1010S or GE 8800), A and B ultrasonography, and skull series. Tomography and contrast arteriography were used when indicated.

Surgical approaches included lateral, anterior, and panoramic orbitotomies, depending on the specific preoperative localisation.

Postoperatively the excised tumour was submitted for light and electron microscopic analysis.

CLINICAL PRESENTATIONS

Of the 7 cases 4 were intraconal and 3 were extraconal. The latter group consisted of the following sites: ethmoid sinus, superior orbit and upper lid, and inferoanterior orbit. Five case histories will be presented.

Case reports

CASE 1

A 60-year-old Caucasian man had noted slowly progressive right proptosis from age 24. There were no other ophthalmic complaints until August 1976, when he complained of blurred vision of his right eye followed by intermittent horizontal diplopia. In addition he had occasional frontal pain and tenderness.

Best corrected right visual acuity was 6/7·5. The right eye was 8 mm proptotic and displaced laterally 2 mm (Fig. 1). The orbit was ballotable and the globe could be retropulsed. He had a right hypertropia of 2 prism dioptres in up gaze and a 4 prism dioptre exotropia in left lateral gaze. The right optic nerve head appeared somewhat pale. The remaining ophthalmic and physical examination was unremarkable.

CT scan showed a smooth, well-defined, oval, intraconal mass lesion in the posterior one-half of the right orbit. It demonstrated mild, uniform enhancement, and a focal area of calcification was seen centrally in the mass (Fig. 2). Orbital *x*-rays were

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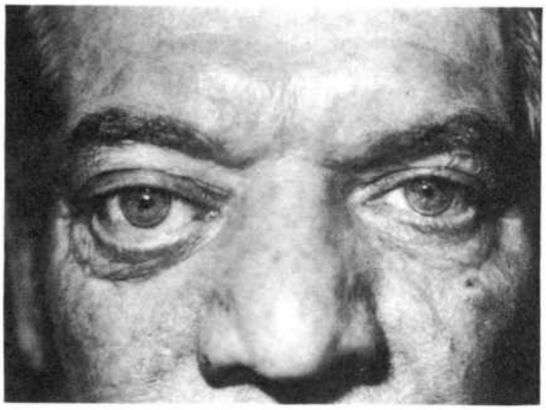

Fig. 1 *Case 1: 60-year-old male with long-standing right proptosis, showing 8 mm axial and 2 mm lateral displacement of the globe.*

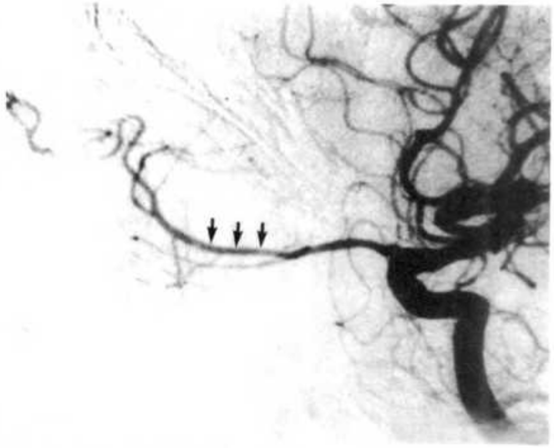

Fig. 3 *Case 1: Carotid arteriogram, subtraction view, demonstrating inferior displacement of ophthalmic artery with no tumour blush.*

normal. Carotid angiography demonstrated inferior displacement of the ophthalmic artery and its lateral branch, with no tumour blush (Fig. 3).

Ultrasonography revealed an intraconal mass lesion with a well-demarcated anterior border. Considerable sound attenuation within the tumour indicated a relatively solid nature. Some cystic areas were also present.

The patient underwent a right lateral orbitotomy. A brown-yellow, encapsulated, multilobular mass was found within the muscle cone beneath the superior rectus muscle and extended medially to lie adjacent to the optic nerve. The tumour had multiple dark varicosities on it, and a large artery branched into the medial surface. Postoperatively the patient recovered uneventfully and has full ocular function without recurrence (Fig. 4).

Light microscopic examination showed a schwannoma with both Antoni types A and B patterns, Verocay bodies, and calcification. The tumour was encapsulated, and abnormal tumour vessels were present with perivascular lymphocytic infiltrates.

CASE 2

A 54-year-old Caucasian woman 1·5 years prior to admission noticed a subjective right central scotoma which she described as a 'white spot and like looking through a heat wave.' Appreciation of fine detail for the right eye diminished after that, and the visual

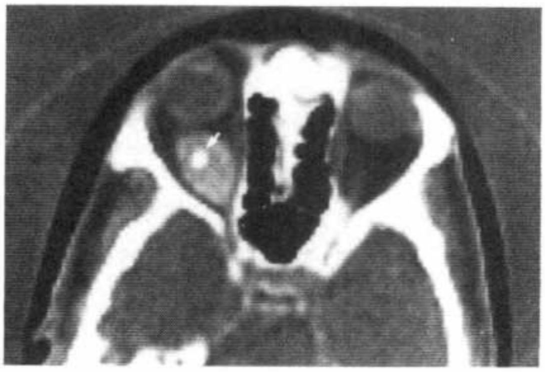

Fig. 2 *Case 1: CT scan (EM 1010s) showing smooth, well defined, oval intraconal mass lesion with central calcification (arrow).*

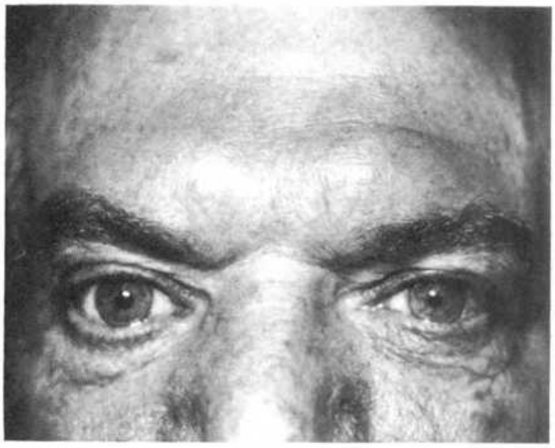

Fig. 4 *Case 1: Postoperative photograph.*

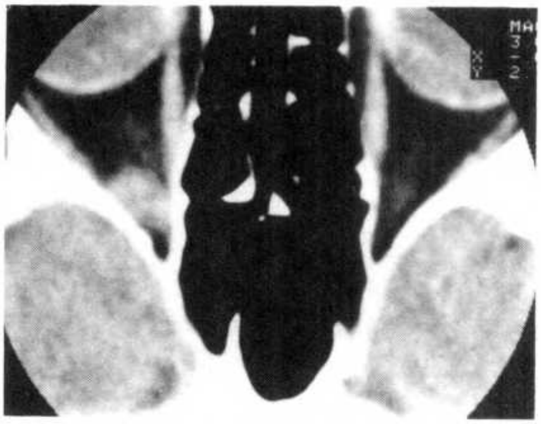

Fig. 5 *Case 2: CT scan (GE 8800) demonstrating apical intraconal lesion.*

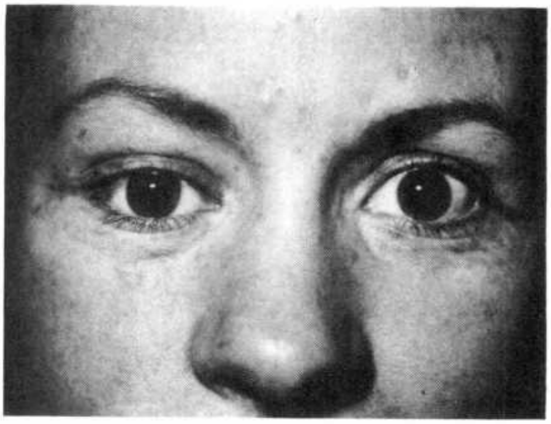

Fig. 6 *Case 3: 32-year-old woman with 4 mm downward displacement of right globe and facial asymmetry.*

acuity was noted to have fluctuated between finger counting and 6/7·5. She denied ocular pain, photophobia, or changes in her facial appearance.

On examination the best corrected visual acuity in her right eye was 6/7·5. The visual field to confrontation was diminished in the right eye. There was a right relative afferent pupillary defect. Ocular and physical examinations were otherwise unremarkable.

CT scan showed a well-defined intraconal lesion in the posterior aspect of the orbit displacing the optic nerve medially (Fig. 5). The posterior margin was well defined and spared the apex. The lesion was approximately 1×2 cm in diameter, and showed a moderate uniform enhancement. No bone destruction was evident. Carotid arteriography did not demonstrate a blush.

Ultrasonography failed to reveal any abnormality.

The patient underwent a combined frontal craniotomy and lateral orbitotomy panoramic approach. An encapsulated lesion 1 cm in diameter was found within the muscle cone at the apex attached to the superior branch of the oculomotor nerve adjacent to the optic nerve. It had fine varicosities on its surface. Because of extreme space limitations it was incised under the microscope, a specimen examined by frozen section, and the remaining mass carefully evacuated leaving the adjacent nerves intact.

Light microscopy showed predominantly Antoni type A schwannoma with many Verocay bodies. Vessels within the tumour had thick walls.

Postoperatively the patient had a partial right ptosis and paresis of the right superior rectus muscle, which remitted completely within the next 6 months.

The remaining intraconal cases had long-standing histories, and the tumours were well encapsulated, did not extend into the apex of the orbit, enhanced mildly on CT scan, and failed to take up contrast on angiography. At surgery they were encapsulated, had varicosities on their surfaces, and were extirpated intact with no postoperative problems. In one a distinct origin from the sixth nerve was noted.

The following 3 cases were extraconal in location.

CASE 3

A 32-year-old Caucasian woman complained of a recent onset of diplopia in up gaze. She had noted abnormality of her right upper lid 8 years prior to admission and was aware of downward displacement of her right globe. Other than flushing of the right side of her face she denied any other orofacial symptoms or evidence of masses elsewhere. On examination she had a number of smooth, mobile, soft masses in her right upper lid which were tender to touch. On the right she showed 4 mm downward displacement of the globe, hemifacial asymmetry, and a hypotropia of 4 prism dioptres, without proptosis (Fig. 6). Visual acuity, pupillary function, visual field, intraocular pressure, and fundus examinations were normal bilaterally. A CT scan done on the EML 1010S scanner did not demonstrate a mass.

An anterior orbitotomy was carried out through a brow incision. A multilobular, yellow, solid tumour mass was identified occupying the entire roof of the orbit (Fig. 7). It extended posteriorly to the apex and appeared to come out of the superior orbital fissure. Numerous nerve-like structures were noted extending from the mass. The bulk of this tumour was removed piecemeal.

Histologically it was a typical schwannoma: encapsulated, Antoni type A, with numerous Verocay bodies with thickened blood vessels cuffed by lymphocytes and plasma cells. Electron microscopy

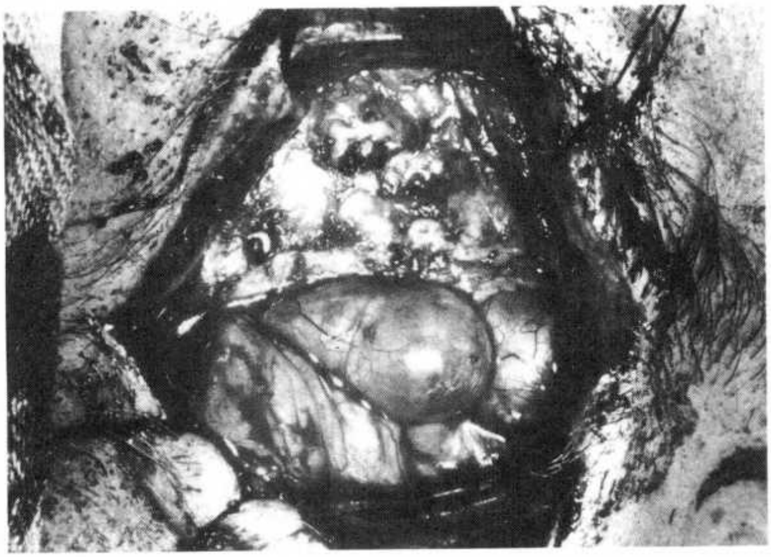

Fig. 7 *Case 3: Anterior orbitotomy showing multilobular, solid tumour mass. Note surface vessels.*

showed many Schwann cells with stacked pale processes surrounded by a well defined basement membrane.

The patient is asymptomatic, has no evidence of recurrence, and no sensory loss in the supraorbital dermatome.

CASE 4

A 24-year-old man noted sudden onset of a constant dull ache in the region of the inner bony margin of his left orbit, associated with a sensation of left retrobulbar pressure. He had a history of chronic nasal discharge and had recently noted left ocular mucopurulent discharge and crusting of the lids on waking.

On examination he had a 4 mm left proptosis and lateral displacement of his globe. Examinations of his pupils, visual acuity, intraocular pressure, and fundi were normal bilaterally. He had diminished nasal air movement and hearing changes compatible with past ear disease.

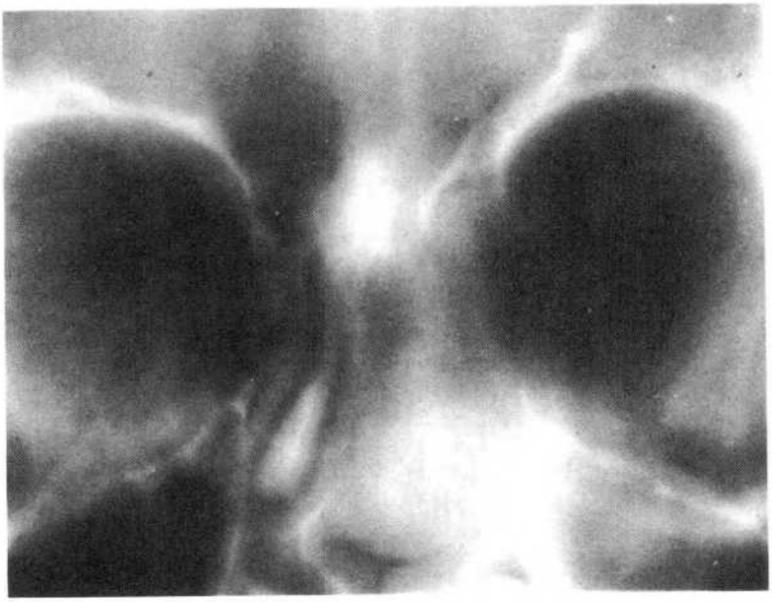

Fig. 8 *Case 4: Polytomogram demonstrates opacification of left frontal, ethmoid, and maxillary sinuses and middle turbinate.*

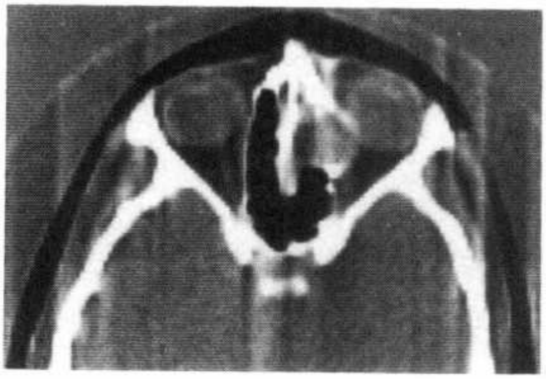

Fig. 9 *Case 4: CT scan (EMI 1010s) showing mass extending from left ethmoid sinus into the medial aspect of the orbit.*

Physical examination was otherwise unremarkable.

Plain films and polytomography showed opacification of the left frontal, ethmoid, and maxillary sinuses, with bone destruction of the medial wall of the orbit (Fig. 8).

A CT scan confirmed opacification of the left ethmoid sinus and adjacent left middle turbinate. A soft tissue mass bulged into the medial aspect of the left orbit with slight indentation of the globe (Fig. 9). The lesion did not enhance.

The preoperative diagnosis was mucocoele of the left ethmoid sinus with pansinusitis.

The patient underwent an ethmoidectomy through a Lynch incision. At surgery the medial wall of the orbit was bowed laterally and showed bony dehiscence. Beneath the bone and within the sinus there was a yellow-pink tumour with a fibrous capsule. It was easily peeled off and removed. Histologically it was typical of schwannoma. The tissue was loosely organised in some areas showing prominent nuclear palisading and numerous Verocay bodies. There was considerable nuclear pleomorphism with some large atypical nuclei. Blood vessels were thickened and hyalinised.

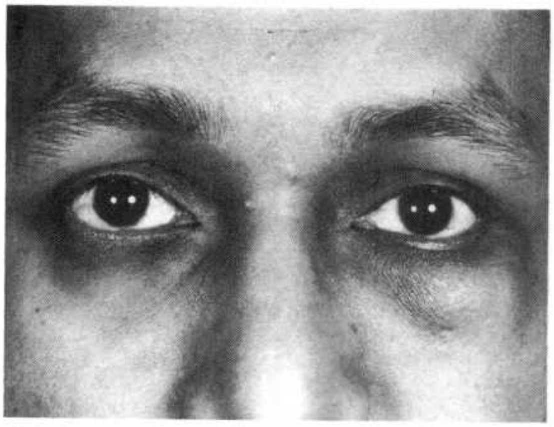

Fig. 10 *Case 5: 31-year-old man with mass involving left lower lid.*

CASE 5

A 31-year-old East Indian man first noted in November 1979 a palpable mass involving the left orbital rim and lower lid. It was associated with a local deep, boring, knife-like pain, occurring once a week, lasting a few minutes, and resolving spontaneously. The lesion grew slowly and was biopsied by a general surgeon in January 1980. The histology was equivocal, with a possible diagnosis of fibrous histiocytoma. Four months later on admission to the Vancouver General Hospital showed a firm, smooth, nontender, immobile mass 23×25 mm involving the left lower lid and extending posteriorly over the inferior orbital margin (Fig. 10). The remainder of his ocular and physical examination was otherwise unremarkable.

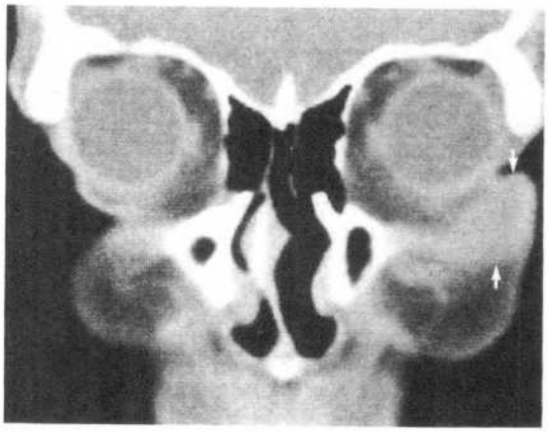

Fig. 11 *Case 5: CT scan (GE 8800) demonstrating thickening of soft tissues anterior to the left infraorbital margin.*

Both axial and coronal CT scans demonstrated thickening of the soft tissues anterior to the left infraorbital margin (Fig. 11). There was no enhancement of this area, and the lesion was not well defined but appeared to be infiltrative in nature. Tomograms of the left orbit showed a slight depression of the inferolateral aspect of the orbital floor with mild localised bony sclerosis, in keeping with a slow-growing soft-tissue mass producing pressure erosion with evidence of bone invasion.

A and B mode ultrasonography showed numerous fine interfaces within a fairly solid mass lesion.

A left anterior orbitotomy revealed a well encapsu-

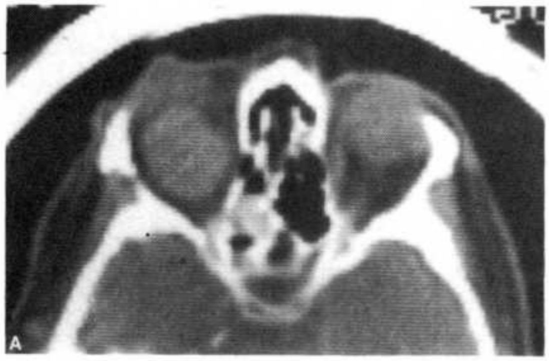

Fig. 12A *CT scan (GE 8800) demonstrating intraconal, well defined mass lesion.*

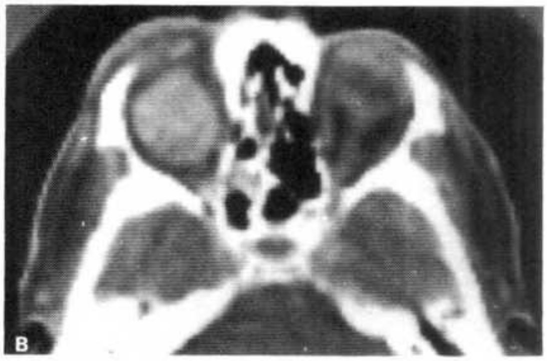

Fig. 12B *Same lesion as Fig. 12A showing mild enhancement following contrast injection.*

lated tumour with abnormal varicose vessels overlying the surface. There were adhesions to the orbital septum and the periosteum of the maxillary bone. The mass appeared to extend from the infraorbital foramen laterally and was stripped from the nerve removing it in toto. Postoperative recovery was complete and uneventful.

Light microscopic examination showed a relatively encapsulated tumour mass with numerous small vascular channels and perivascular lymphocytic cuffing. The cells were both spindle and stellate shaped, arranged in a variety of patterns. Some were noted to be loosely entwined within a myxoid-appearing stroma, while others were more compactly arranged in a streaming formation. In some sections a dense, homogeneous, eosinophilic, collagenous stroma was noted. Electron microscopic findings supported the diagnosis of a fibrous schwannoma.

Results

All 7 patients had histologically confirmed schwannomas. None had systemic manifestations of neurofibromatosis. Their ages at the time of presentation ranged from the third to seventh decades. The tumour sites were 4 intraconal and 3 extraconal. Of the latter, one was in the ethmoid sinus, another anterior to the infraorbital margin, and one involved the superior orbit and upper lid. Displacement of the affected globe was related to the site of the mass and ranged from marked anteroinferolateral to none at all. Visual acuity on presentation was uniformly 6/7·5 or better except for one case having acuity of 6/12 (due to macular degeneration).

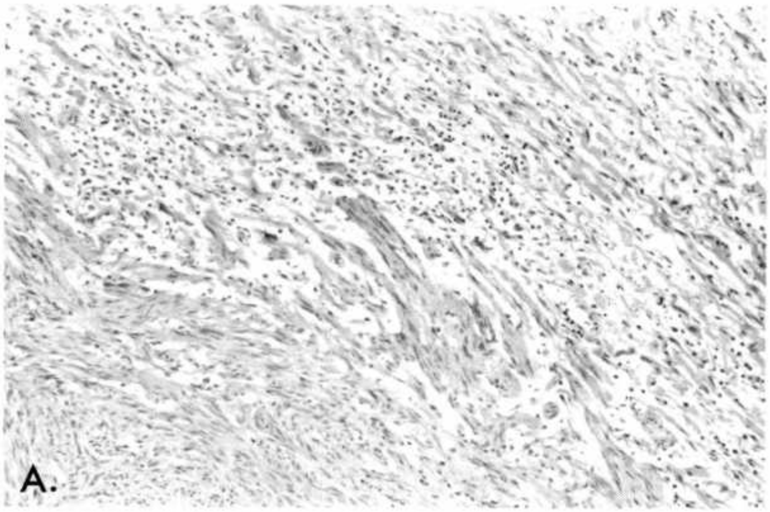

Fig. 13A *Histopathology of an intraconal schwannoma demonstrating an admixture of compactly arranged interlacing fascicles (Antoni A pattern—lower right) and more loosely arranged cells separated by a clear matrix (Antoni B pattern) with a background of lymphocytoid cells. (Haematoxylin and eosin, ×44).*

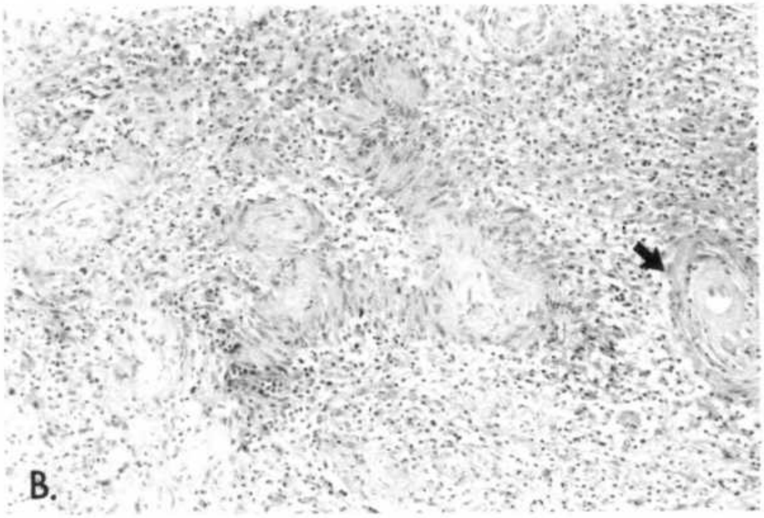

Fig. 13B *Histopathology of another area of the same tumour showing a hyalinised vessel (arrow) with an organoid cellular pattern centrally (Verocay body). Background pattern is basically Antoni B with lymphocytoid and lipid laden foam cells. (H. and E. ×44).*

Diplopia and strabismus on a mechanical basis were noted in 2 patients. Only one patient had an abnormal funduscopic examination with choroidal striae and peripapillary haemorrhages.

All patients were investigated by CT scanning, which detected 6 of the 7 lesions. Of these, 4 were intraconal, one was in the infraorbital soft tissues, and one was in the ethmoid sinus and middle turbinate with extension into the medial aspect of the orbit. Two tumours caused medial displacement of the optic nerve, 3 caused axial proptosis, and one caused indentation of the globe. Four of 5 contrast CT studies demonstrated enhancement, which was of a mild degree (Figs. 12A, B). In all cases except one the lesions were well defined with discrete edges. The shape varied from round to oval. One case had associated bony indentation and one had calcification in the central part of the tumour. The intraconal lesions did not follow a muscle or mimic muscle enlargement, nor did they extend into and obscure the orbital apex.

Ultrasonography was carried out in 4 of 7 patients, all of whom had intraconal lesions. Of these, 3 were detected. All were described as encapsulated, solid lesions with a well demarcated anterior border. Within the mass were a number of tissue interfaces which attenuated dramatically. A posterior border could not be detected.

At surgery the lesions were characteristically yellowish-tan in colour, solid, encapsulated, and had

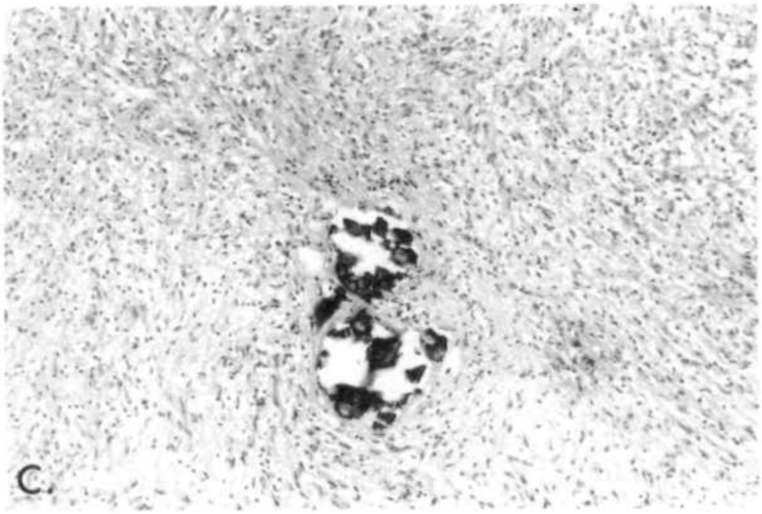

Fig. 13C *Case 1: Light microscopy of tumour from case 1 showing a basically Antoni B pattern with a central area of calcification. (H. and E., ×44).*

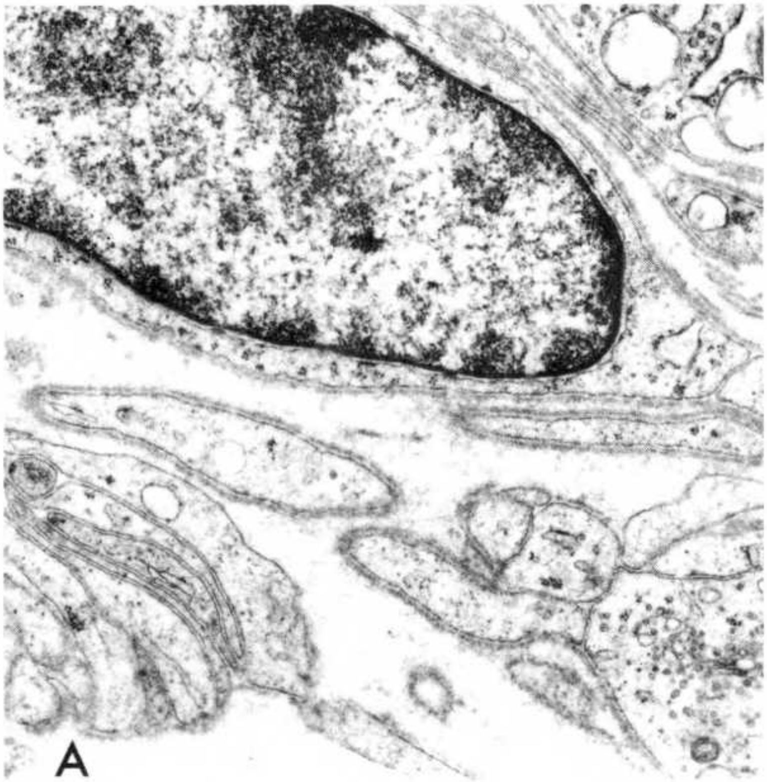

Fig. 14A *Case 3: Electron micrograph of tissue from case 3 showing Schwann cells with interdigitating and convoluted cell membranes with few subcellular organelles and a prominent extracellular basement membrane. (× 18 110).*

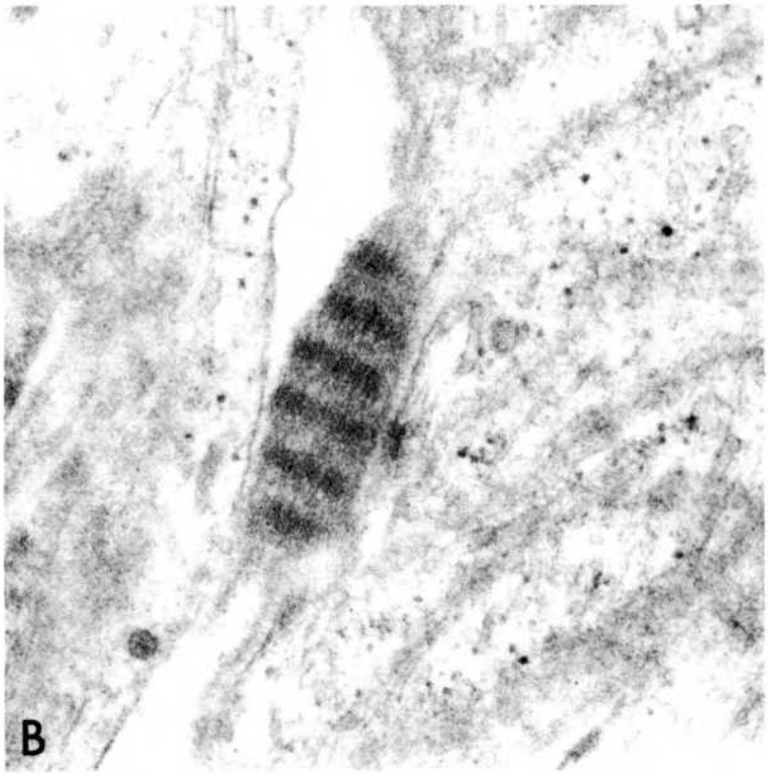

Fig. 14B *Electron micrograph from an intraconal schwannoma shown in Fig. 14A. This demonstrates 'long spacing' collagen adjacent to a cell membrane (× 50 700).*

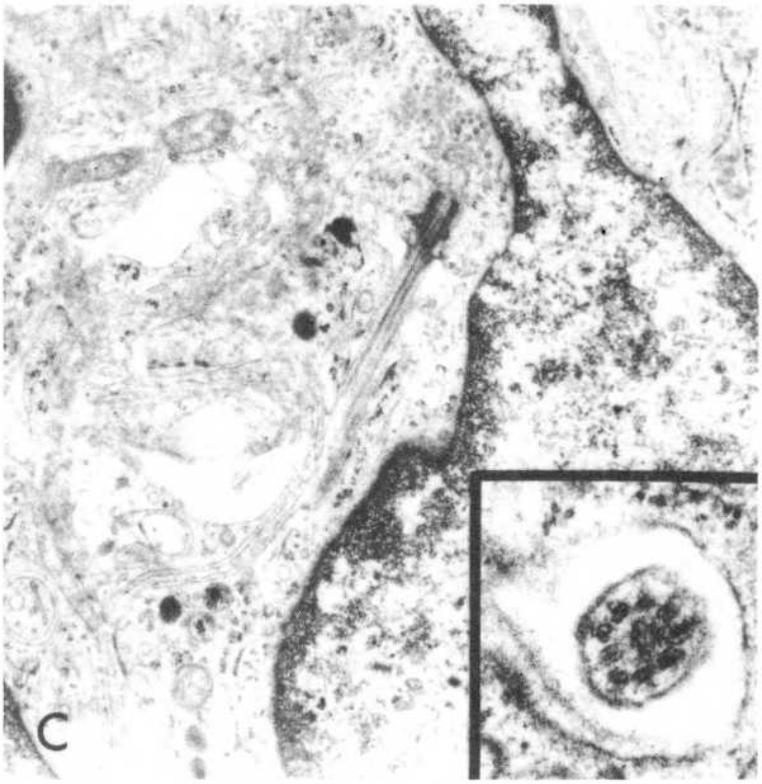

Fig. 14C *Case 2: Electron micrograph from the lesion described in case 2. Note adjacent to the nuclear membrane is a longitudinal section of a cilia (× 8500). Insert shows a cilium in cross section (× 66 000).*

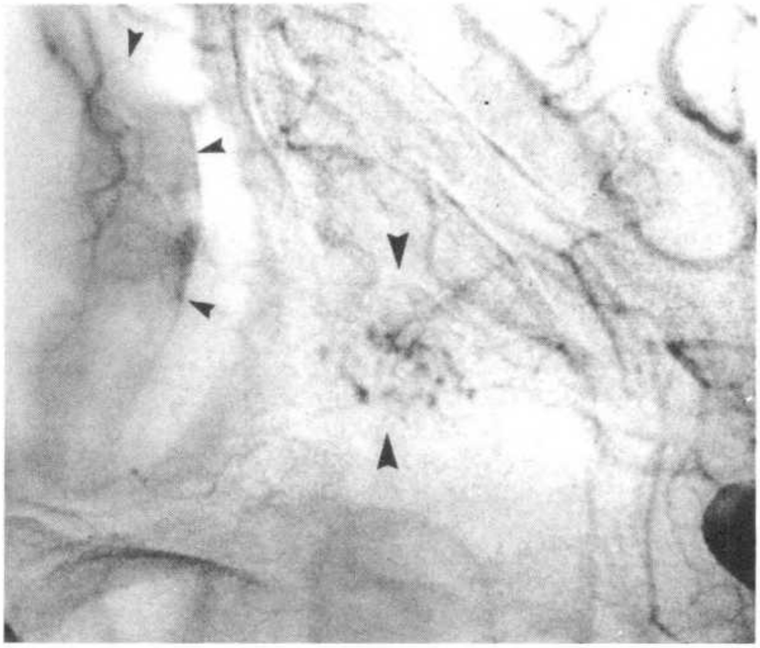

Fig. 15 *Carotid arteriogram, subtraction view, of histologically proved cavernous haemangioma showing late minor pooling of dye (between large arrowhead). Small arrowheads define the choroidal crescent.*

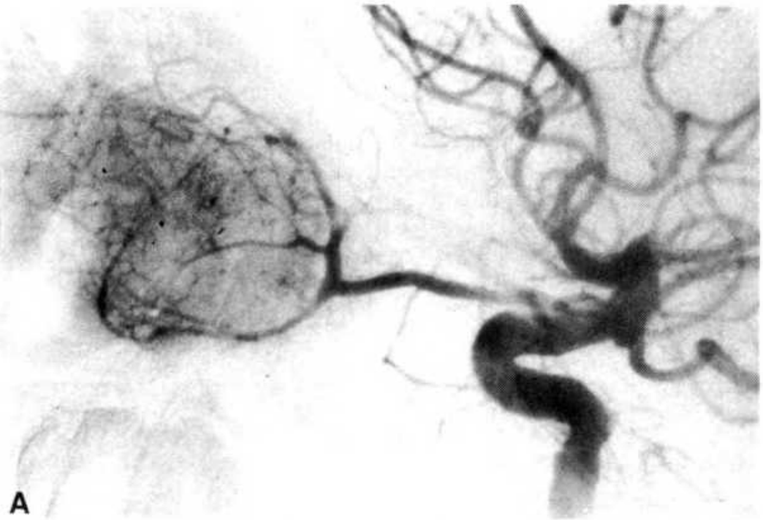

Fig. 16A *Early phase, carotid arteriogram, subtraction view, of histologically proved optic nerve meningioma demonstrating multiple tumour vessels.*

typical varicose, violaceous tumour vessels on their surface. Four nerves were specifically identified in association with their respective lesions, all of which were removed leaving the nerves of origin intact. The associated nerves were: superior division of the third, sixth, infraorbital, and superior division of the ophthalmic nerve.

Histology was variable but typical of schwannoma, including mixed Antoni type A and B patterns (Fig. 13A), tumour capsule, thick walled hyalinised vessels (Fig. 13B), perivascular lymphocytic cuffing, calcification (Fig. 13C), organoid arrangements of Schwann cells with Verocay bodies (Fig. 13B), loose collagenous stroma, and occasional nuclear pleomorphism. Electron microscopy confirmed the schwannian origin in each of the tumours (Fig. 14A). Long spaced collagen was identified in one of the tumours only (Fig. 14B). An unusual electron microscopic feature noted in one of the tumours was the presence of a typical cilia (Fig. 14C).

Discussion

Primary schwannoma rarely occurs in the orbit. Although no single feature is pathognomonic, a multiplicity of clinical, radiographic, and surgical features point to the diagnosis of this lesion. It is a disease primarily of adults, has an insidious onset, is slow growing, and is noninvasive with minimal effect on other orbital structures. The range of clinical

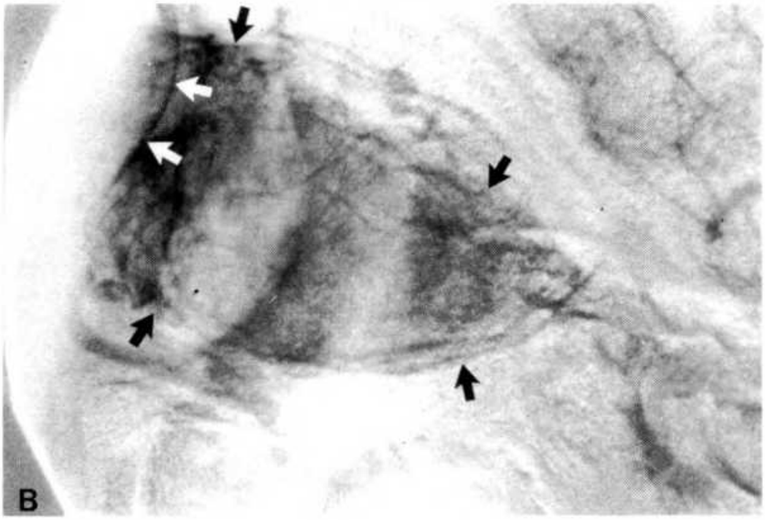

Fig. 16B *Same lesion, late phase, demonstrating tumour blush (black arrows); white arrows indicate choroidal crescent.*

presentation in our patients included optic neuropathy, proptosis, diplopia, anterior orbital mass, and sinusitis. Of available investigations CT scan was found to be the most useful, particularly in localising the lesion, whether within the orbit or extending into it from periorbital soft tissues or paranasal sinuses. The configuration varies from round to oval, and the tumour generally has a well-defined margin and, if intraconal, is well demarcated posteriorly. On CT scan most lesions enhanced to a mild degree, but on carotid arteriography there is no uptake of dye. Ultrasonography confirmed the presence of a discrete, encapsulated, solid-mass lesion. Other slow growing orbital tumours to be considered in the differential diagnosis are cavernous haemangioma, meningioma, and haemangiopericytoma. In our experience, on carotid arteriography, cavernous haemangiomas show late minor pooling of the dye (Fig. 15), while meningiomas have multiple tumour vessels and a late blush (Fig. 16A, B). Haemangiopericytomas have an early florid blush. These 3 lesions when compared with schwannomas showed more marked enhancement with contrast on CT scanning. In addition, on CT scanning schwannomas tend not to follow a muscle or mimic muscle enlargement as is seen in thyroid ophthalmopathy, nor do the lesions extend into and obscure the apex of the orbit, as may be seen in orbital pseudotumour or intrinsic optic nerve lesions.[4-7] Although previous series[8-11] all describe lesions of large size, a high index of suspicion, accurate localisation, and determination of size by the methods described here allow small, symptom-causing lesions to be treated early and successfully, as demonstrated in case 2. Primary orbital schwannomas are typically benign, encapsulated, noninvasive tumours. Thus surgical excision as a definitive therapy is indicated.

The surgical approach, whether anterior, lateral, or combined lateral-orbitotomy and frontal-craniotomy, was dictated by the location of the lesions as determined by preoperative investigations. Surgical removal may be total or subtotal, in piecemeal fashion, or by evacuation of the tumour from within its capsule. The type of removal is dictated by the location and attachments to adjacent structures. Because of the peripheral outpouching characteristic of schwannomas they may be successfully stripped of the nerve of origin by microscopic techniques. Like other authors, in a follow-up ranging from 6 months to 5 years we have had no recurrences.[8-10]

Histological examination also showed the variability of the tumours.[2,3] Antoni types A and B were found in addition to more fibrous types and some areas of cellular pleomorphism. Electron microscopy confirmed the Schwann cell origin in all cases and was typical of Schwann cell tumours previously described.[2] The unusual finding of cilia in one case is not a specific feature of schwannomas but has been described in many tumours of both epithelial and mesenchymal origin.[12]

In conclusion, primary orbital schwannomas are a rare orbital and periorbital tumour with variable anatomical and histological expressions. Preoperative differential diagnosis of a slow-growing soft tissue orbital or periorbital mass includes schwannoma. Although CT scan is helpful in localising and identifying the lesion, no single pathognomonic investigative procedure or feature exists. Rather a constellation of features point to this diagnosis. Surgical excision is indicated and to date has been successful.

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British Journal of Ophthalmology, 1982, **66**, 183–185

Extracapsular cataract extraction—some problems

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SUMMARY Comments are made on the method of removing the anterior capsule during the performance of extracapsular cataract operations. The difficulty of performing this manoeuvre adequately is emphasised. Observations carried out during the postoperative period by means of the slit-lamp revealed some hitherto undescribed changes in the capsule. The edge of the anterior capsule can be clearly seen and looks like broken glass. Fine fibrils have been observed attached to the fractured capsular edge. In the early postoperative period the anterior capsule tends to be separated from the posterior by quite a deep space, but at an early stage, usually about the fourth day, the edge of the anterior capsule becomes adherent to the posterior capsule, and rather rapidly a dense fibrous line forms along the joint.

We have been through a period in ophthalmology in the 1950s and 1960s when extracapsular cataract extraction had practically ceased—so much so that there is now a whole generation of ophthalmologists who have hardly been taught how to express a nucleus. Extracapsular cataract extraction is a very old operation, the first description being by Jaques Daviel in 1753.[1] The after-cataract which tends to form in the scaffolding of the remnants of capsule and lens matter has been extensively studied by Soemmering[2] and many others. Duke-Elder[3] stated that in Soemmering's ring the edges of the anterior capsule adhere to the posterior but that fibrous cells may be laid down on the posterior capsule by fibroblasts from the iris. Furthermore, the subcapsular epithelium comes to line the ring—both anterior and posterior capsules. Bladder cells, Elschnig's pearls,[4] and their possible removal by irrigation are also mentioned.

The indications for extracapsular surgery are present in any case of cataract where for some reason intracapsular extraction is thought to be hazardous or unsuitable. Absolute indications would be when the patient is below the age of 40 years, where later drainage surgery is contemplated, or where iridocapsular pseudophakos is planned. Relative indications would be patients between the ages of 40 and 60, patients with high myopia, and patients in whom ischaemic retinopathy is suspected.

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Material and methods

The eyes of patients undergoing routine extracapsular cataract surgery at the Western Ophthalmic Hospital were observed during the year 1980. Particular attention was given to the slit-lamp appearances in the early postoperative period, and photographs were taken of the anterior capsule where appropriate on the second, fourth, and several subsequent days. In addition some photographs were taken during the course of extracapsular surgery in the operating theatre.

The surgical technique consisted in the forming of a limbal groove ab externo, the insertion of 3 preplaced sutures, and puncture of the anterior capsule with a hooked blue disposable needle attached to a drip of Hartmann's solution. The section was then opened and removal of the anterior capsule carried out, usually with Arruga's capsule forceps.

We tried to ensure that the removal of the anterior capsule should be as complete as possible, because while removing anterior capsule one is probably also removing active subcapsular epithelium and minimising the chance of after-cataract. (There have been recent pronouncements on the subjects of anterior capsular removal following the upsurge of interest consequent on phakoemulsification and pseudophakos. For example, Arnott[5] recommended cutting the capsule in the shape of an inverted Christmas tree, the 'tree' being drawn out by fine toothed forceps, and Kelman[6] advised an approxi-

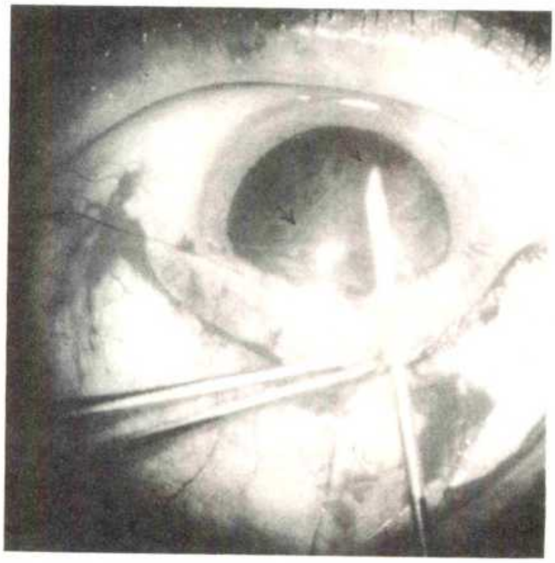

Fig. 1 *While the capsule is being cut with a hooked blue needle, it tends to split in a linear fashion. Arrows indicate edge of split capsule.*

mately similar manoeuvre carried out under an air bubble.)

After removal of capsule the nucleus was expressed and the wound temporarily closed by tying the sutures in bows. Irrigation-aspiration by a double cannula could then be carried out at leisure as in the closed technique, and at the conclusion of this procedure, or sometimes before it, a peripheral iridectomy was performed. Finally the bows were tied permanently or were undone and retied later if it was intended to insert an intraocular lenticulus.

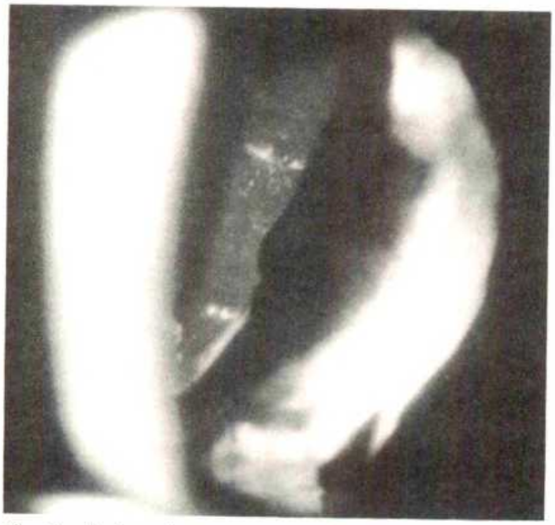

Fig. 2 *Broken-glass appearance of anterior capsule remnants 2 days postoperatively.*

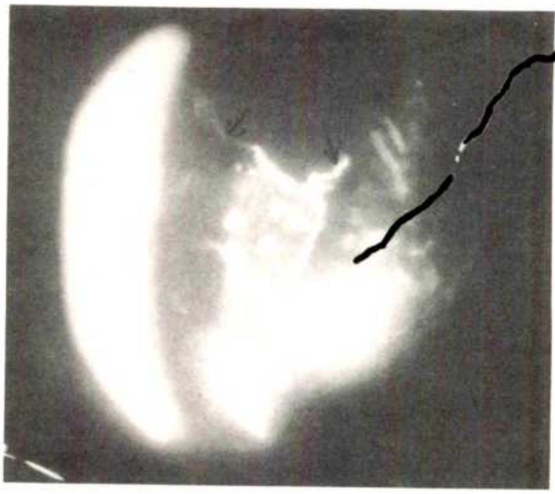

Fig. 3 *Fibres 'growing' from edge of cut capsule 2 days postoperatively. Normally the fibres are very fine; these appear to have an opaque coagulum on them making them more visible than usual.*

Results

We found that the anterior capsule tended to split in an erratic fashion, like tearing Cellophane, once it was pricked with a hooked blue needle—and the direction of the split was difficult to control. Furthermore, unless the microscope was zoomed up to a high magnification it was very difficult to see what was happening (Fig. 1). However, in many cases the capsule could be divided in a fairly satisfactory manner, hooked or rolled up towards the section, and eventually grasped with forceps, cut, and removed. It was important to include cutting in this procedure, since if pure traction was used it was possible to pull out the capsular rug from under the nucleus.

After lens extraction the edge of the anterior capsule could be seen in the anterior chamber looking very like broken glass (Fig. 2).

At an early stage—certainly within 3 days—fine fibrils appeared to be growing out of the fractured edge, though it was not clear whether they were only existing lens fibres whose position had been disrupted by the surgery (Fig. 3).

In 3 to 4 more days the anterior capsular edge moved backwards and became adherent to the posterior capsule. It was doubtful whether it was drawn backwards by contracture of the previously mentioned fibrils, which may first have become attached to the posterior capsule, or whether the

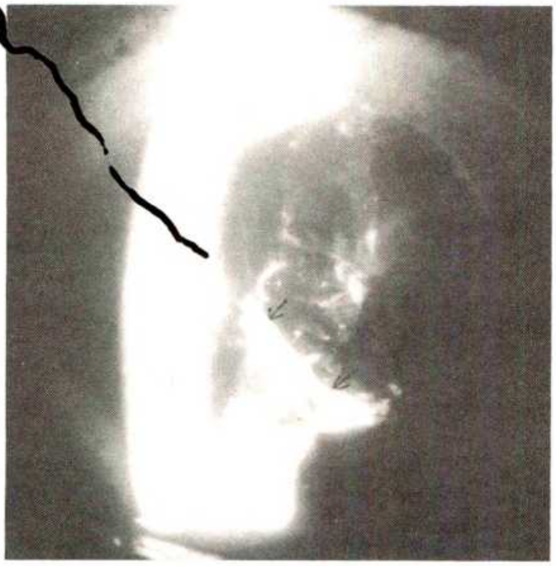

Fig. 4 *The anterior and posterior capsules rapidly unite: arrow indicates junction.*

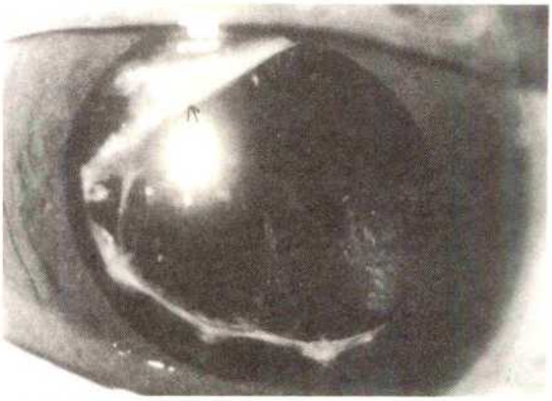

Fig. 5 *One year after extracapsular extraction (fellow eye of Fig. 4). The approximately annular line of junction between anterior and posterior capsules marked by dense fibrous tissue can be clearly seen.*

backward movement was a chance one resulting from swirling currents in the anterior chamber, the adhesion to the posterior capsule being possibly mediated by the fibrils (Fig. 4). After a little longer the line of junction between the edge of the anterior capsular remnant and the intact posterior capsule became marked by dense fibrous tissue. It seems likely that this tissue is the successor to the fine fibrils originally noted, so that the mechanism mentioned by Duke-Elder of fibroblasts originating from the iris is probably incorrect. A question which interests us is why lens cells sometimes form dense fibrous bands and at other times the clear bladder cells with which we are familiar. The fibrous bands tend to form preferentially at the broken edge of the anterior capsule where it becomes tied down to the posterior capsule (Fig. 5).

Discussion

The main point of this paper is to draw attention to the hitherto undescribed changes in the position of the anterior lens capsule immediately following surgery and also to mention the fine fibrils sometimes found on the capsular edge. It is uncertain whether these changes will prove to have any particular clinical or histopathological significance, but further extended observations on the behaviour of the anterior capsule may possibly yield some more interesting information.

We should like to emphasise in conclusion that we believe removal of the anterior lens capsule over as extensive an area as possible is the key to success in cataract surgery and that manoeuvres such as polishing the posterior capsule and even the exceptionally careful and complete removal of cortical material are of less importance than the removal of anterior capsule as efficiently as possible.

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British Journal of Ophthalmology, 1982, **66**, 186–189

Bilateral proptosis, dilatation of conjunctival veins, and papilloedema: a neuro-ophthalmological syndrome caused by arteriovenous malformation of the torcular Herophili

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SUMMARY A patient with an occipital dural arteriovenous malformation (AVM) developed signs of a carotid-cavernous sinus fistula and raised intracranial pressure. Bilateral transverse sinus occlusion associated with the AVM produced these signs by rerouting intracranial venous drainage anteriorly through the cavernous sinuses and superior ophthalmic veins. Angiography and computerised tomographic reformation techniques were used to define these extraordinary cranio-orbital venous pathways.

Orbital and ocular signs of a carotid-cavernous sinus fistula can be produced by any posteriorly located arteriovenous malformation (AVM) draining anteriorly into the orbital venous system.[1-9] Ocular signs of raised intracranial pressure (ICP) can be produced by any intracranial AVM that causes a rise of pressure in the posterior dural sinuses.[10]

We report major alterations in cerebral, dural, and orbital venous systems, confirmed by angiography and computerised tomography (CT), in a patient whose AVM at the torcular Herophili (confluence of superior sagittal, straight, and transverse sinuses) caused a clinical syndrome of bilateral proptosis, dilated conjunctival veins, and papilloedema.

Case report

This 25-year-old woman had a 4-year history of raised ICP that was caused by a dural AVM of the torcular Herophili. In August 1979 she noted proptosis of the

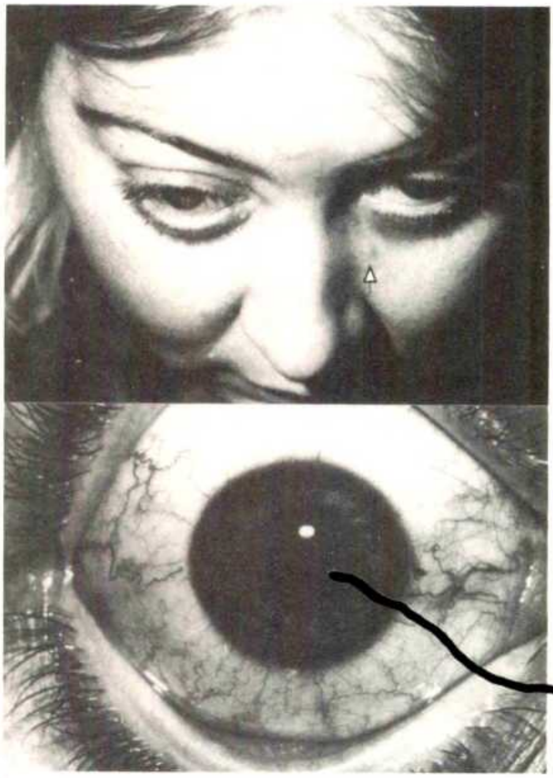

Fig. 1 Top: *Face photograph showing bilateral asymmetrical proptosis (exophthalmometer readings right 25 mm, left 22 mm) and enlarged left angular vein (arrow).* Bottom: *Right eye showing dilated conjunctival veins.*

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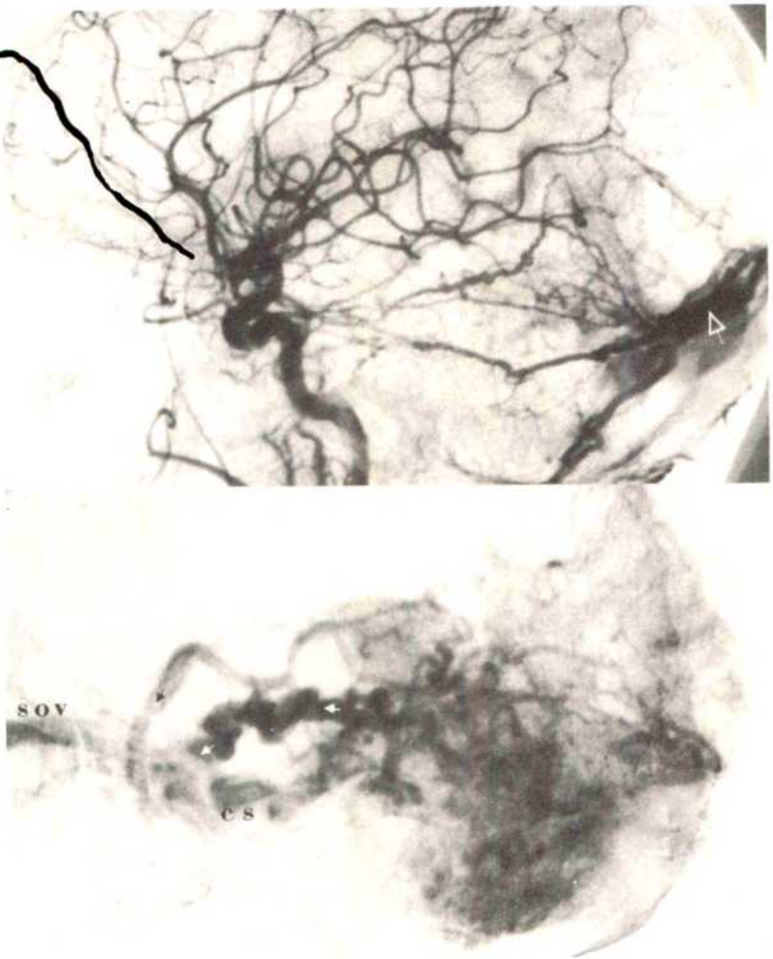

Fig. 2 Top: *Common carotid angiogram showing the torcular AVM (arrow), with feeder vessels from the occipital artery, posterior branches of the middle meningeal artery, and meningeal branches of the internal carotid artery.* Bottom: *Venous drainage of the malformation through the superficial middle cerebral vein (above), and deep cerebral veins (below), into the cavernous sinus (CS) and superior ophthalmic vein (SOV) (small arrows indicate direction of flow).*

right eye, redness of both eyes, and increasing headaches. Her visual acuity was 6/6 bilaterally, and she had asymmetrical proptosis that was bilateral, but more marked on the right (Fig. 1, top), dilated conjunctival vessels in both eyes (Fig. 1, bottom), and a prominent angular vein on the right. Intraocular pressures were normal. She had chronic papilloedema bilaterally and a partial homonymous hemianopia of the left visual field.

Selective carotid and vertebral angiography showed an occipital dural AVM with feeding vessels from the right and left occipital arteries, the posterior branches of the right and left meningeal arteries, and tentorial branches of the right and left internal carotid arteries (Fig. 2, top). Both transverse venous sinuses were totally occluded. Venous drainage from the AVM and from the brain flowed in a retrograde direction (Fig. 2, bottom) through: (1) the straight sinus, the vein of Galen, and deep cerebral veins; (2) the superior sagittal sinus and the superficial middle cerebral veins; (3) the meningeal veins.

These venous pathways and all others from within the skull entered the cavernous sinuses and the superior ophthalmic veins. The latter veins were markedly dilated (Fig. 3, top).

Axial CT scans showed portions of the occipital AVM, as well as the dilated basal veins and the anterior extensions of these veins toward the anterior cavernous sinuses.

By means of a research 'trace programme' (General Electrical Medical Systems, Milwaukee, Wisconsin, USA) vertical reformations along the wandering path of the dilated and contrast-enhanced veins in the basal cisterns permitted accurate identification of the point at which the enlarged basal veins penetrated the dura around the cavernous sinus, the superior orbital fissure, and entered the orbit (Fig. 4). In addition the CT scans of the orbit showed enlargement of the optic nerves secondary to dilatation of the vaginal sheath spaces (Fig. 3, bottom).

Radical resection of the dural AVM relieved the elevated pressure in the retrograde venous outflow channels at the base of the brain in the cavernous sinuses and in the orbital venous system. The patient's proptosis resolved, and the conjunctival redness and papilloedema disappeared.

Discussion

When posteriorly located dural AVMs cause bilateral transverse sinus occlusion,[11] a major rerouting of venous blood from the head must occur. Blood shunted through the AVM flows anteriorly in a retrograde direction through the basal, cortical, and dural veins toward the cavernous sinus. As exemplified by the CT and angiographic findings in the patient we describe, the basal veins become grotesquely enlarged, their calibre exceeding that of the carotid arteries. Before they pierce the dura of the anterior cavernous sinus they occupy a position first adjacent and just lateral to the optic nerves and chiasm, and then lateral and inferior to the anterior clinoid processes.

In the absence of adequate alternative venous outflow channels from the cavernous sinus, blood from the basal veins, together with blood from the sphenoparietal and cavernous sinuses, flows in a retrograde manner into the orbital venous bed. As a result orbital veins dilate, and the patient develops bilateral proptosis and dilated conjunctival vessels, thus simulating the features of a carotid-cavernous sinus fistula. These signs, together with evidence of raised ICP, including papilloedema, constitute an unusual neuro-ophthalmic syndrome suggesting a dural AVM with major sinus occlusion.

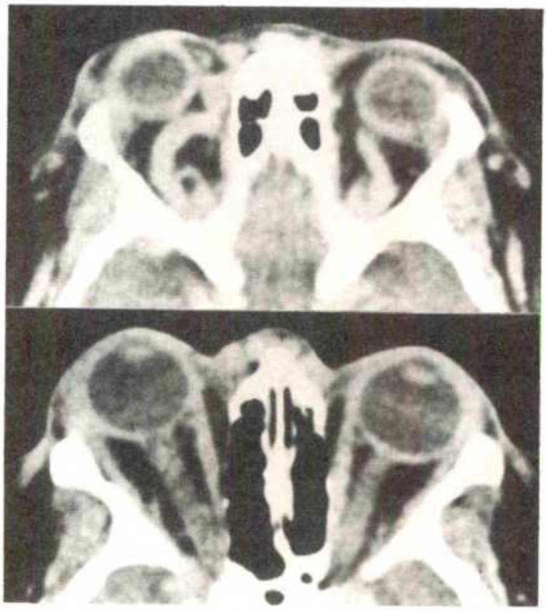

Fig. 3 Top: *Axial computerised tomography scan showing trace programme along a contrast-enhanced basal vein.* Bottom: *Lateral view of vertical reformation of same vein.*

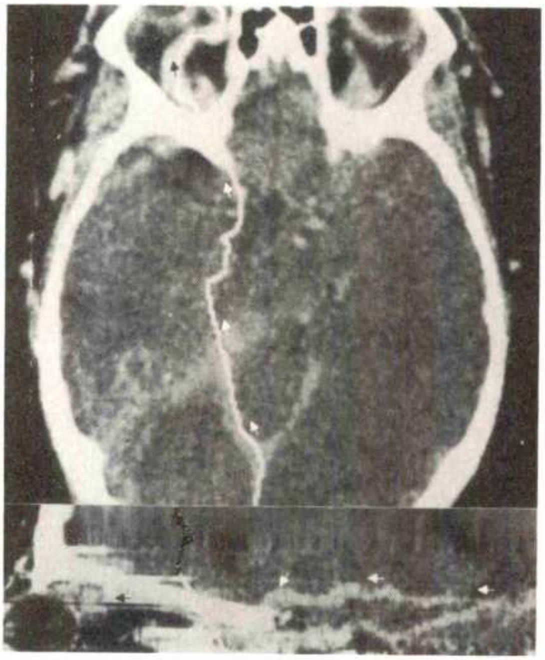

Fig. 4 Top: *Postcontrast axial computerised tomography scan showing markedly dilated superior ophthalmic veins.* Bottom: *Postcontrast axial scan indicating enlarged optic nerve sheaths.*

This study was supported in part by fellowship grants from the Royal College of Surgeons of England, Keeler Instruments, Ltd. (UK), and the Eastern Health and Social Services Board, Northern Ireland.

The authors thank Dr Michael Edwards for referring the patient to us, Susan Eastwood for excellent editorial assistance, and Beverly McGehee for preparation of the manuscript.

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British Journal of Ophthalmology, 1982, **66**, 190–193

Liposarcoma of the orbit: a clinicopathological case report

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SUMMARY Liposarcoma is a very rare primary tumour of the orbit. The present report describes changes seen by computed tomography, carotid angiography, and histopathology and gives a review of the literature.

Liposarcoma is an uncommon mesenchymal tumour. It shows a preference for certain locations such as the lower limbs and the retroperitoneal region.[1] In the orbit only a few cases of histopathologically verified liposarcomas have been reported. It is the object of this report to describe an additional case of primary liposarcoma of the orbit and to give a review of the literature.

Case report

In August 1977 the patient, a 58-year-old woman, was admitted to the University Eye Clinic in Uppsala with painless left-sided exophthalmos of almost one year's duration. Apart from 5 mm protrusion of the left eye she had no clinical abnormalities. Plain *x*-ray of the orbit was normal. Computed tomography (CT), however, revealed a tumour mass in the mediolateral part of the left orbit (Fig. 1). The attenuation in the tumour varied in different parts, with CT-numbers ranging from +5 to +15 Hounsfield units (HU). Following intravenous contrast injection (60 ml Isopaque Cerebral, Nyco, Oslo, Norway) there was a moderate increase in attenuation, with CT numbers between +20 and +30 HU. By carotid angiography the tumour was seen to be supplied by small branches from the ophthalmic artery, and the tumour displayed a marked blush in the venous phase (Fig. 2a, b). A fine-needle apiration biopsy contained regular endothelial cells of normal appearance, whereas pathological cell forms were lacking. At surgery a firm and lobulated tumour was easily removed by lateral orbitotomy. The postoperative period was uncomplicated. The patient has been followed up for 3½ years and she has not shown any clinical or CT signs of tumour recurrence.

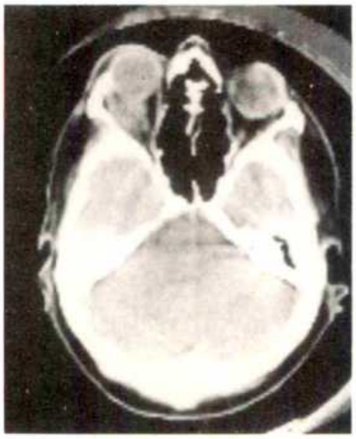

Fig. 1 *CT scan showing large retrobulbar tumour in the left orbit and marked exophthalmos.*

OPHTHALMIC PATHOLOGY

The tumour measured 33×27×27 mm. It had a firm consistency and a greyish to yellowish cut surface. Histologically the tumour showed both loose and solid areas. In the loose areas the predominant cell type was a rather small spindle to stellate cell with poorly defined boundaries. The nuclei were small and dense, giving an impression of pyknosis. The cells were loosely arranged in a slightly eosinophilic mucoid matrix (Fig. 3a) which stained weakly with alcian blue stain and colloid iron stain. It was weakly metachromatic with toluidine blue. After digestion with testicular hyaluronidase for 2 hours at 37°C

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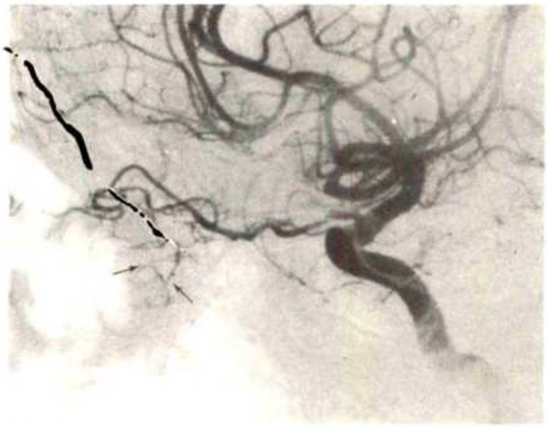

Fig. 2a

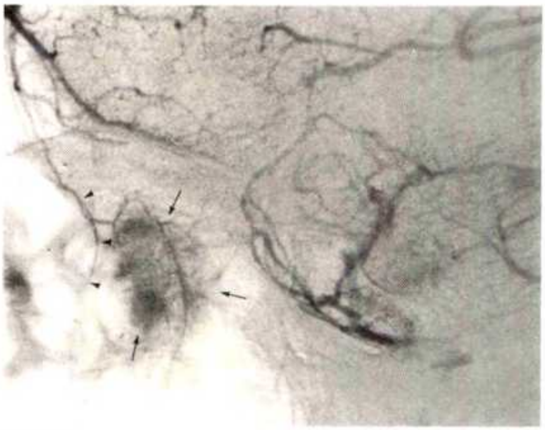

Fig. 2b

Fig. 2 *Internal carotid angiography.* (a) *The arterial phase shows delicate tumour vessels (arrows) from the ophthalmic artery.* (b) *The venous phase shows tumour blush (arrows). The position of the eye globe is seen by the contrast enhancement of the choroid (wedges).*

neither of the stain were positive, thus indicating that the background material consisted mainly of acid mucopolysaccharides. In the periphery of the mucoid areas there was a successive transition into areas with immature lipocytes (Fig. 3b). These cells showed more definite cytoplasmic borders and their cytoplasm contained coarse vacuoles. The round or oval nuclei showed obvious polymorphism and were placed either centrally or peripherally in the tumour cells. Mitosis or bizarre cell nuclei were not observed.

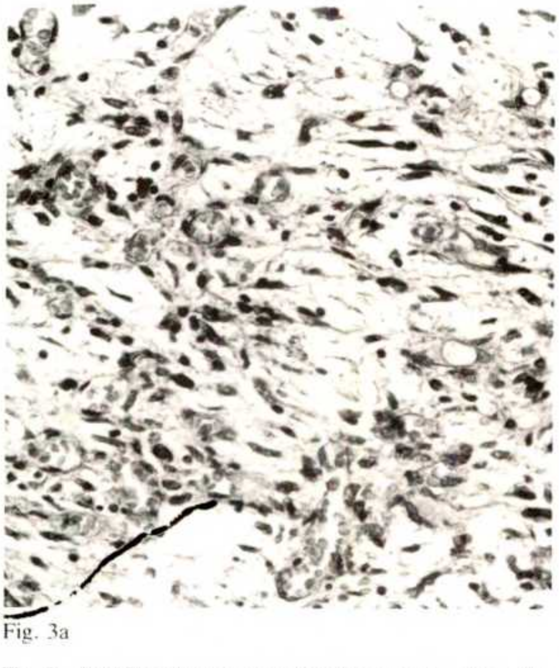

Fig. 3a

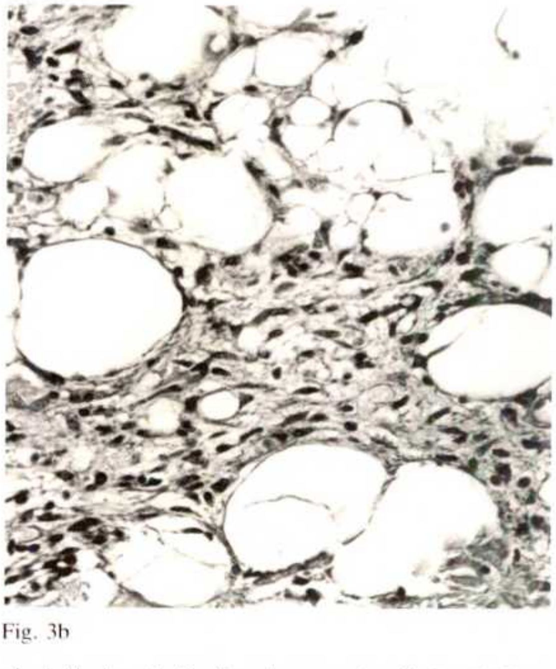

Fig. 3b

Fig. 3 (a) *Myxomatous area of the liposarcoma with stellate and spindle shaped cells. Note the maze of capillaries.* (b) *Part of the tumour showing lipocytes in different stages of maturation. (HE, ×240).*

In some areas there was a successive change of the cells into mature lipocytes. The solid areas were built up by fibrotic strands crossing through the tumour tissue. The lipocytes stained bright red with scarlet red and black with Sudan black. The lipid drops varied in size from very small to coarse in the immature cells, whereas only large drops filled the mature lipocytes. Throughout the whole tumour there was a rich capillary network. This was most prominent in the areas showing the lowest degree of cellular differentiation. Large vessels were rare. The tumour had a pseudocapsule of condensed tumour cells as its outer limit.

In accordance with the histopathological findings the tumour was diagnosed as a well differentiated myxoid liposarcoma of the orbit.

Discussion

Liposarcomas of the orbit are very rare tumours and to our knowledge only 11 cases have been reported.[2–11] Various authors[3,4,12,13] have classified these tumours. According to the classification by Enzinger *et al.*,[13] which was accepted as the WHO classification of 1969, 4 different types of liposarcomas may be separated, namely, myxoid, embryonal round cell, well differentiated, and pleomorphic. In the present case the histological diagnosis of myxoid liposarcoma was based on the presence of proliferating lipocytes in various stages of differentiation, the myxoid hyaluronidase-sensitive acid mucopolysaccharides, and the prominent capillary network. In the previously reported cases the myxoid type has been predominant.

The examination by CT revealed a retrobulbar tumour with mixed attenuation. The CT characteristics of this kind of tumour located in the orbit has not to our knowledge been described hitherto. The CT characteristics of liposarcoma in other regions such as extremities, mediastinum, and retroperitoneum have been reported.[14–16] In these cases there was a wide range in attenuation values of the tumours (from −90 to +30 HU), and in some cases with low attenuation values the fatty origin of the tumour could be predicted from the CT scan. However, the attenuation in the present tumour did not indicate the lipomatous character of the mass.

Carotid angiography showed a highly vascularised tumour. Several angiographic patterns of liposarcomas have been described,[17–20] but they did not differ from those seen in other malignant tumours.

Fine-needle aspiration has been shown to be of great help in diagnosing orbital tumours.[21] In the present case only endothelial cells were obtained and a definitive diagnosis could not be made. However, in view of the maze of capillaries in the tumour this finding is not surprising.

Radical surgery is generally regarded as the treatment of choice for liposarcoma. Jones and Jakobiec[11] described 2 cases of orbital liposarcoma which both primarily had no other therapy than surgery. In both these cases there were clinical signs of recurrence of the tumour one year later. In the case of liposarcoma reported by Schroeder *et al.*[10] 2 years passed before there were clinical signs of tumour recurrence. In these 3 cases radiation therapy was given after the recurring tumour had been removed by orbital exenteration. In the present case the patient has been followed up for 3½ years postoperatively and she has not shown any signs of tumour recurrence clinically or by CT. According to Schäfer and Wellens[19] radiation therapy should always be given to liposarcomas irrespective of the histological diagnosis. In cases of myxoid liposarcomas irradiation alone may be curative. Cytostatic drugs are recommended only in cases with metastases, where a rate of remission of 40% has been reported.[22]

In retrospect it seems that the prognosis of orbital liposarcomas is rather favourable and that the tumour may not recur after orbital exenteration combined with irradiation and finally chemotherapy.

The skilled technical assistance of Margareta Björling and Cristina Bittkowski is gratefully acknowledged.

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British Journal of Ophthalmology, 1982, **66**, 194–204

Primary orbital schwannomas

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SUMMARY Seven histologically proved cases of primary orbital schwannoma have been seen at the University of British Columbia Orbital Clinic between September 1976 and December 1980. We describe here their varied clinical presentations, preoperative investigations, operative findings, and appearances on light and electron microscopy. Although no single feature is pathognomonic, a multiplicity of clinical, radiographic, and surgical features point to this lesion. Of preoperative investigations the computed tomography scan was the most helpful, especially in localising the lesion. Of the 7, 4 were intraconal and 3 were extraconal. The surgical approach was dictated by tumour site and included anterior, lateral, and panoramic orbitotomies. At surgery the nerve of origin of 4 of the tumours was identified. All tumours were excised totally or subtotally. There has been no recurrence to date.

Schwannomas account for 1% of orbital tumours[1 2] and may arise anywhere within or adjacent to the orbit.[3] We have seen 7 histologically proved cases of schwannomas in the Orbital Clinic at the University of British Columbia between September 1976 and December 1980. We describe here their varied clinical presentations, preoperative investigations, operative findings, and appearances on light and electron microscopy.

Materials and methods

During the period from September 1976 to December 1980 484 cases were seen in the Orbital Clinic at the University of British Columbia, of which 123 represented mass lesions. Seven of these were found to be schwannomas, representing 1·4% of all orbital cases seen and 5·7% of mass lesions.

Diagnostic investigations included computed tomography (CT) scan (EMI 1010S or GE 8800), A and B ultrasonography, and skull series. Tomography and contrast arteriography were used when indicated.

Surgical approaches included lateral, anterior, and panoramic orbitotomies, depending on the specific preoperative localisation.

Postoperatively the excised tumour was submitted for light and electron microscopic analysis.

CLINICAL PRESENTATIONS

Of the 7 cases 4 were intraconal and 3 were extraconal. The latter group consisted of the following sites: ethmoid sinus, superior orbit and upper lid, and inferoanterior orbit. Five case histories will be presented.

Case reports

CASE 1

A 60-year-old Caucasian man had noted slowly progressive right proptosis from age 24. There were no other ophthalmic complaints until August 1976, when he complained of blurred vision of his right eye followed by intermittent horizontal diplopia. In addition he had occasional frontal pain and tenderness.

Best corrected right visual acuity was 6/7·5. The right eye was 8 mm proptotic and displaced laterally 2 mm (Fig. 1). The orbit was ballotable and the globe could be retropulsed. He had a right hypertropia of 2 prism dioptres in up gaze and a 4 prism dioptre exotropia in left lateral gaze. The right optic nerve head appeared somewhat pale. The remaining ophthalmic and physical examination was unremarkable.

CT scan showed a smooth, well-defined, oval, intraconal mass lesion in the posterior one-half of the right orbit. It demonstrated mild, uniform enhancement, and a focal area of calcification was seen centrally in the mass (Fig. 2). Orbital *x*-rays were

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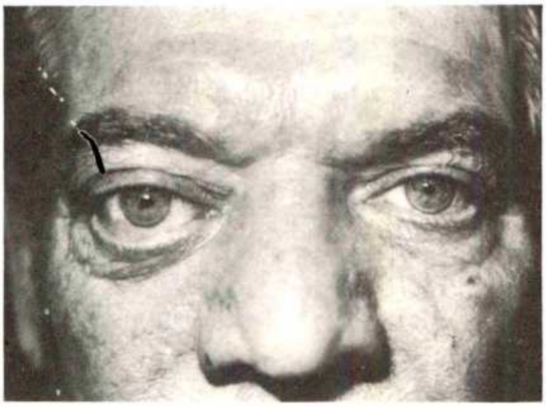

Fig. 1 *Case 1: 60-year-old male with long-standing right proptosis, showing 8 mm axial and 2 mm lateral displacement of the globe.*

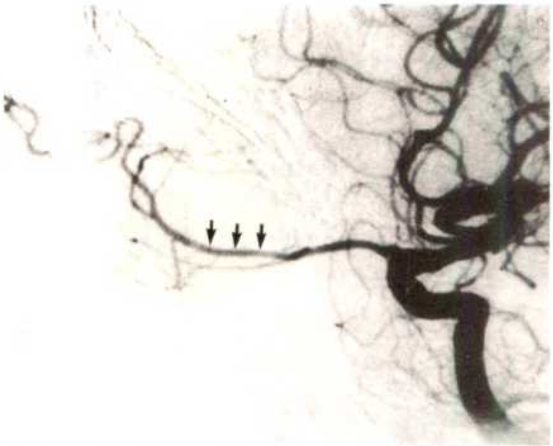

Fig. 3 *Case 1: Carotid arteriogram, subtraction view, demonstrating inferior displacement of ophthalmic artery with no tumour blush.*

normal. Carotid angiography demonstrated inferior displacement of the ophthalmic artery and its lateral branch, with no tumour blush (Fig. 3).

Ultrasonography revealed an intraconal mass lesion with a well-demarcated anterior border. Considerable sound attenuation within the tumour indicated a relatively solid nature. Some cystic areas were also present.

The patient underwent a right lateral orbitotomy. A brown-yellow, encapsulated, multilobular mass was found within the muscle cone beneath the superior rectus muscle and extended medially to lie adjacent to the optic nerve. The tumour had multiple dark varicosities on it, and a large artery branched into the medial surface. Postoperatively the patient recovered uneventfully and has full ocular function without recurrence (Fig. 4).

Light microscopic examination showed a schwannoma with both Antoni types A and B patterns, Verocay bodies, and calcification. The tumour was encapsulated, and abnormal tumour vessels were present with perivascular lymphocytic infiltrates.

CASE 2

A 54-year-old Caucasian woman 1·5 years prior to admission noticed a subjective right central scotoma which she described as a 'white spot and like looking through a heat wave.' Appreciation of fine detail for the right eye diminished after that, and the visual

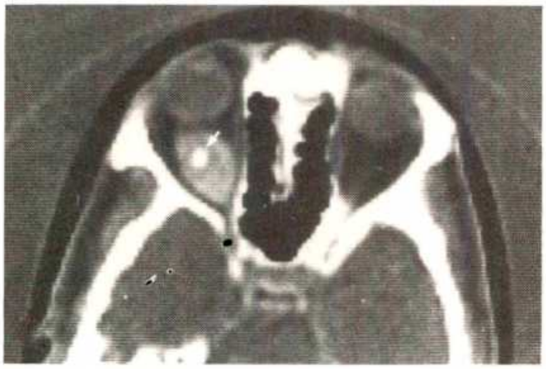

Fig. 2 *Case 1: CT scan (EM 1010s) showing smooth, well defined, oval intraconal mass lesion with central calcification (arrow).*

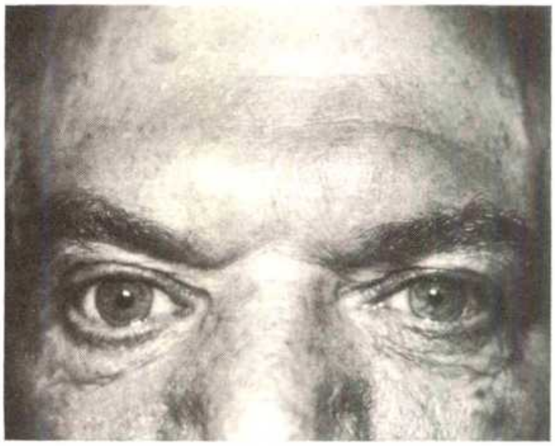

Fig. 4 *Case 1: Postoperative photograph.*

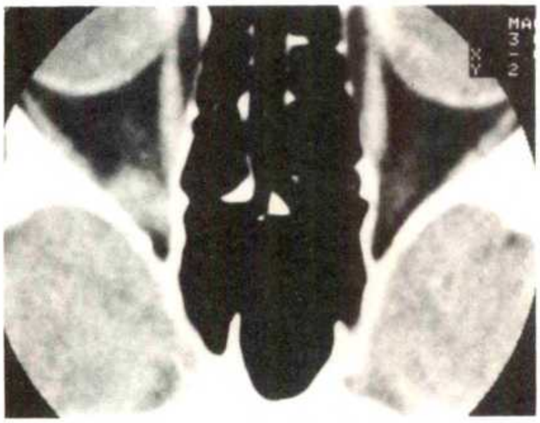

Fig. 5 *Case 2: CT scan (GE 8800) demonstrating apical intraconal lesion.*

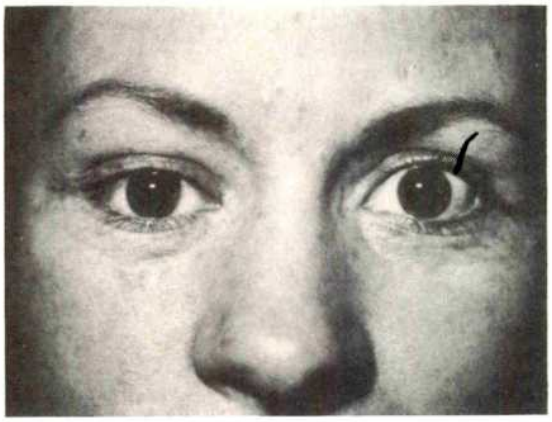

Fig. 6 *Case 3: 32-year-old woman with 4 mm downward displacement of right globe and facial asymmetry.*

acuity was noted to have fluctuated between finger counting and 6/7·5. She denied ocular pain, photophobia, or changes in her facial appearance.

On examination the best corrected visual acuity in her right eye was 6/7·5. The visual field to confrontation was diminished in the right eye. There was a right relative afferent pupillary defect. Ocular and physical examinations were otherwise unremarkable.

CT scan showed a well-defined intraconal lesion in the posterior aspect of the orbit displacing the optic nerve medially (Fig. 5). The posterior margin was well defined and spared the apex. The lesion was approximately 1×2 cm in diameter, and showed a moderate uniform enhancement. No bone destruction was evident. Carotid arteriography did not demonstrate a blush.

Ultrasonography failed to reveal any abnormality.

The patient underwent a combined frontal craniotomy and lateral orbitotomy panoramic approach. An encapsulated lesion 1 cm in diameter was found within the muscle cone at the apex attached to the superior branch of the oculomotor nerve adjacent to the optic nerve. It had fine varicosities on its surface. Because of extreme space limitations it was incised under the microscope, a specimen examined by frozen section, and the remaining mass carefully evacuated leaving the adjacent nerves intact.

Light microscopy showed predominantly Antoni type A schwannoma with many Verocay bodies. Vessels within the tumour had thick walls.

Postoperatively the patient had a partial right ptosis and paresis of the right superior rectus muscle, which remitted completely within the next 6 months.

The remaining intraconal cases had long-standing histories, and the tumours were well encapsulated, did not extend into the apex of the orbit, enhanced mildly on CT scan, and failed to take up contrast on angiography. At surgery they were encapsulated, had varicosities on their surfaces, and were extirpated intact with no postoperative problems. In one a distinct origin from the sixth nerve was noted.

The following 3 cases were extraconal in location.

CASE 3

A 32-year-old Caucasian woman complained of a recent onset of diplopia in up gaze. She had noted abnormality of her right upper lid 8 years prior to admission and was aware of downward displacement of her right globe. Other than flushing of the right side of her face she denied any other orofacial symptoms or evidence of masses elsewhere. On examination she had a number of smooth, mobile, soft masses in her right upper lid which were tender to touch. On the right she showed 4 mm downward displacement of the globe, hemifacial asymmetry, and a hypotropia of 4 prism dioptres, without proptosis (Fig. 6). Visual acuity, pupillary function, visual field, intraocular pressure, and fundus examinations were normal bilaterally. A CT scan done on the EML 1010S scanner did not demonstrate a mass.

An anterior orbitotomy was carried out through a brow incision. A multilobular, yellow, solid tumour mass was identified occupying the entire roof of the orbit (Fig. 7). It extended posteriorly to the apex and appeared to come out of the superior orbital fissure. Numerous nerve-like structures were noted extending from the mass. The bulk of this tumour was removed piecemeal.

Histologically it was a typical schwannoma: encapsulated, Antoni type A, with numerous Verocay bodies with thickened blood vessels cuffed by lymphocytes and plasma cells. Electron microscopy

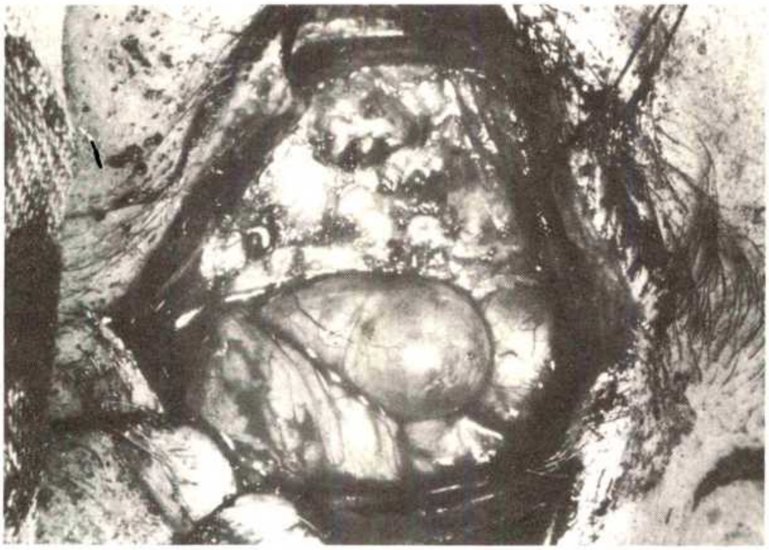

Fig. 7 *Case 3: Anterior orbitotomy showing multilobular, solid tumour mass. Note surface vessels.*

showed many Schwann cells with stacked pale processes surrounded by a well defined basement membrane.

The patient is asymptomatic, has no evidence of recurrence, and no sensory loss in the supraorbital dermatome.

CASE 4

A 24-year-old man noted sudden onset of a constant dull ache in the region of the inner bony margin of his left orbit, associated with a sensation of left retrobulbar pressure. He had a history of chronic nasal discharge and had recently noted left ocular mucopurulent discharge and crusting of the lids on waking.

On examination he had a 4 mm left proptosis and lateral displacement of his globe. Examinations of his pupils, visual acuity, intraocular pressure, and fundi were normal bilaterally. He had diminished nasal air movement and hearing changes compatible with past ear disease.

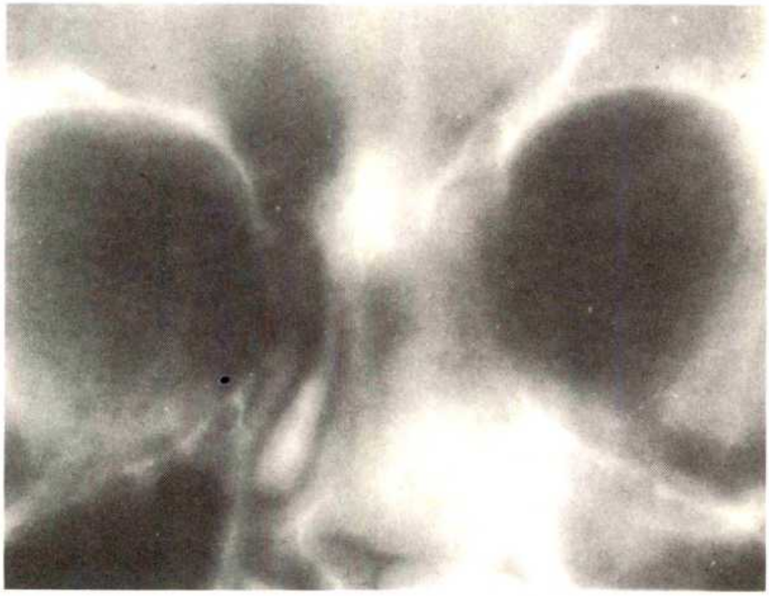

Fig. 8 *Case 4: Polytomogram demonstrates opacification of left frontal, ethmoid, and maxillary sinuses and middle turbinate.*

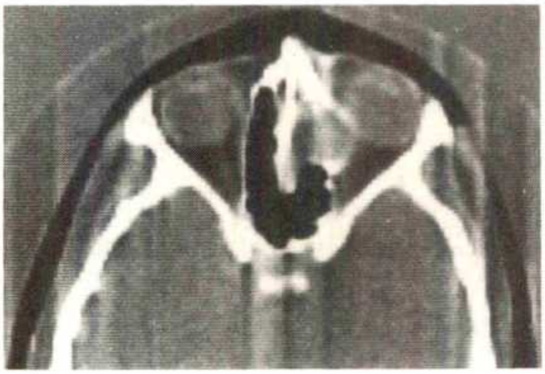

Fig. 9 *Case 4: CT scan (EMI 1010s) showing mass extending from left ethmoid sinus into the medial aspect of the orbit.*

Physical examination was otherwise unremarkable.

Plain films and polytomography showed opacification of the left frontal, ethmoid, and maxillary sinuses, with bone destruction of the medial wall of the orbit (Fig. 8).

A CT scan confirmed opacification of the left ethmoid sinus and adjacent left middle turbinate. A soft tissue mass bulged into the medial aspect of the left orbit with slight indentation of the globe (Fig. 9). The lesion did not enhance.

The preoperative diagnosis was mucocoele of the left ethmoid sinus with pansinusitis.

The patient underwent an ethmoidectomy through a Lynch incision. At surgery the medial wall of the orbit was bowed laterally and showed bony dehiscence. Beneath the bone and within the sinus there was a yellow-pink tumour with a fibrous capsule. It was easily peeled off and removed. Histologically it was typical of schwannoma. The tissue was loosely organised in some areas showing prominent nuclear palisading and numerous Verocay bodies. There was considerable nuclear pleomorphism with some large atypical nuclei. Blood vessels were thickened and hyalinised.

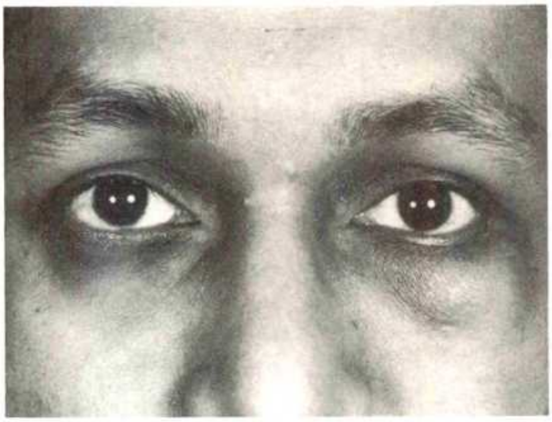

Fig. 10 *Case 5: 31-year-old man with mass involving left lower lid.*

CASE 5

A 31-year-old East Indian man first noted in November 1979 a palpable mass involving the left orbital rim and lower lid. It was associated with a local deep, boring, knife-like pain, occurring once a week, lasting a few minutes, and resolving spontaneously. The lesion grew slowly and was biopsied by a general surgeon in January 1980. The histology was equivocal, with a possible diagnosis of fibrous histiocytoma. Four months later on admission to the Vancouver General Hospital showed a firm, smooth, nontender, immobile mass 23×25 mm involving the left lower lid and extending posteriorly over the inferior orbital margin (Fig. 10). The remainder of his ocular and physical examination was otherwise unremarkable.

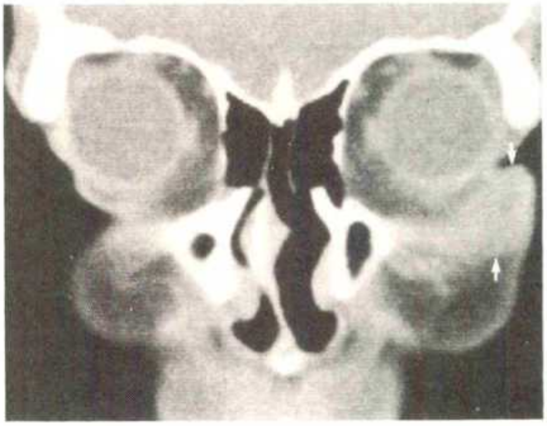

Fig. 11 *Case 5: CT scan (GE 8800) demonstrating thickening of soft tissues anterior to the left infraorbital margin.*

Both axial and coronal CT scans demonstrated thickening of the soft tissues anterior to the left infraorbital margin (Fig. 11). There was no enhancement of this area, and the lesion was not well defined but appeared to be infiltrative in nature. Tomograms of the left orbit showed a slight depression of the inferolateral aspect of the orbital floor with mild localised bony sclerosis, in keeping with a slow-growing soft-tissue mass producing pressure erosion with evidence of bone invasion.

A and B mode ultrasonography showed numerous fine interfaces within a fairly solid mass lesion.

A left anterior orbitotomy revealed a well encapsu-

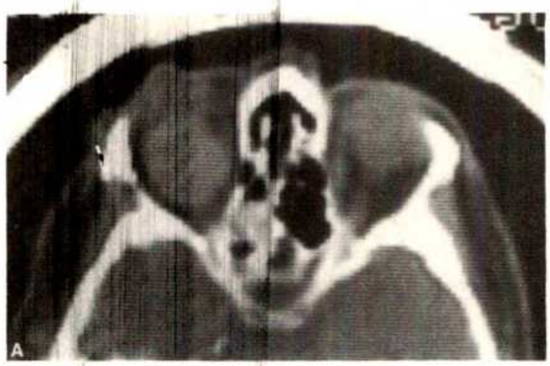

Fig. 12A *CT scan (GE 8800) demonstrating intraconal, well defined mass lesion.*

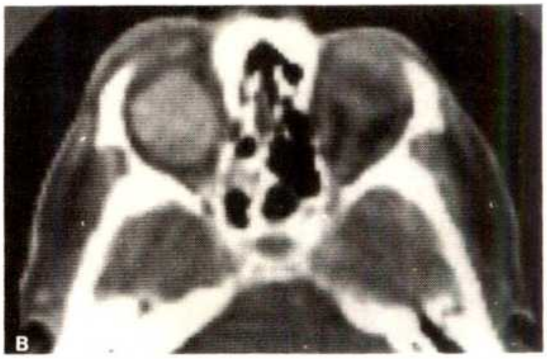

Fig. 12B *Same lesion as Fig. 12A showing mild enhancement following contrast injection.*

lated tumour with abnormal varicose vessels overlying the surface. There were adhesions to the orbital septum and the periosteum of the maxillary bone. The mass appeared to extend from the infraorbital foramen laterally and was stripped from the nerve removing it in toto. Postoperative recovery was complete and uneventful.

Light microscopic examination showed a relatively encapsulated tumour mass with numerous small vascular channels and perivascular lymphocytic cuffing. The cells were both spindle and stellate shaped, arranged in a variety of patterns. Some were noted to be loosely entwined within a myxoid-appearing stroma, while others were more compactly arranged in a streaming formation. In some sections a dense, homogeneous, eosinophilic, collagenous stroma was noted. Electron microscopic findings supported the diagnosis of a fibrous schwannoma.

Results

All 7 patients had histologically confirmed schwannomas. None had systemic manifestations of neurofibromatosis. Their ages at the time of presentation ranged from the third to seventh decades. The tumour sites were 4 intraconal and 3 extraconal. Of the latter, one was in the ethmoid sinus, another anterior to the infraorbital margin, and one involved the superior orbit and upper lid. Displacement of the affected globe was related to the site of the mass and ranged from marked anteroinferolateral to none at all. Visual acuity on presentation was uniformly 6/7·5 or better except for one case having acuity of 6/12 (due to macular degeneration).

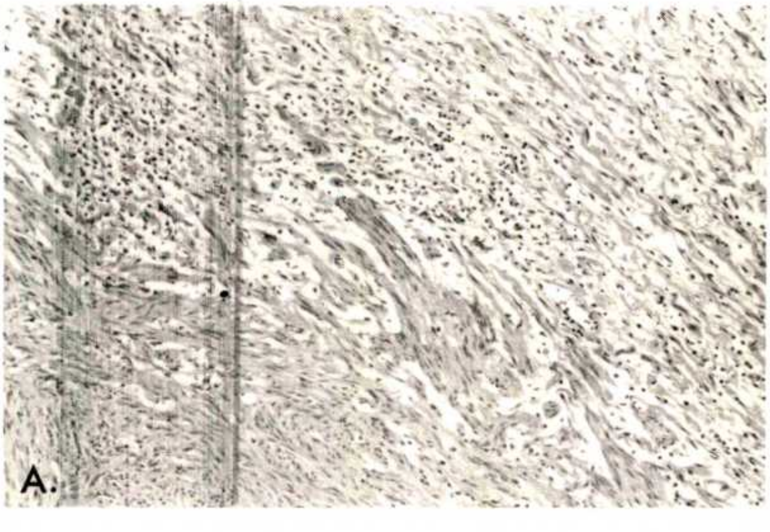

Fig. 13A *Histopathology of an intraconal schwannoma demonstrating an admixture of compactly arranged interlacing fascicles (Antoni A pattern—lower right) and more loosely arranged cells separated by a clear matrix (Antoni B pattern) with a background of lymphocytoid cells. (Haematoxylin and eosin, ×44).*

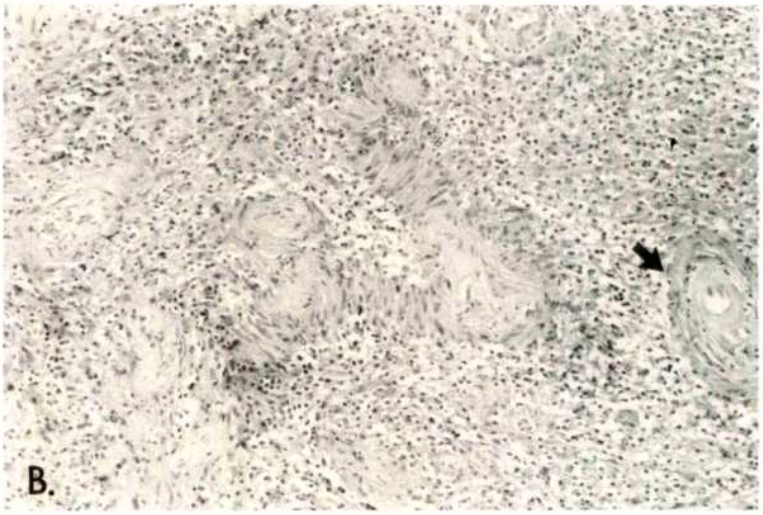

Fig. 13B *Histopathology of another area of the same tumour showing a hyalinised vessel (arrow) with an organoid cellular pattern centrally (Verocay body). Background pattern is basically Antoni B with lymphocytoid and lipid laden foam cells. (H. and E. ×44).*

Diplopia and strabismus on a mechanical basis were noted in 2 patients. Only one patient had an abnormal funduscopic examination with choroidal striae and peripapillary haemorrhages.

All patients were investigated by CT scanning, which detected 6 of the 7 lesions. Of these, 4 were intraconal, one was in the infraorbital soft tissues, and one was in the ethmoid sinus and middle turbinate with extension into the medial aspect of the orbit. Two tumours caused medial displacement of the optic nerve, 3 caused axial proptosis, and one caused indentation of the globe. Four of 5 contrast CT studies demonstrated enhancement, which was of a mild degree (Figs. 12A, B). In all cases except one the lesions were well defined with discrete edges. The shape varied from round to oval. One case had associated bony indentation and one had calcification in the central part of the tumour. The intraconal lesions did not follow a muscle or mimic muscle enlargement, nor did they extend into and obscure the orbital apex.

Ultrasonography was carried out in 4 of 7 patients, all of whom had intraconal lesions. Of these, 3 were detected. All were described as encapsulated, solid lesions with a well demarcated anterior border. Within the mass were a number of tissue interfaces which attenuated dramatically. A posterior border could not be detected.

At surgery the lesions were characteristically yellowish-tan in colour, solid, encapsulated, and had

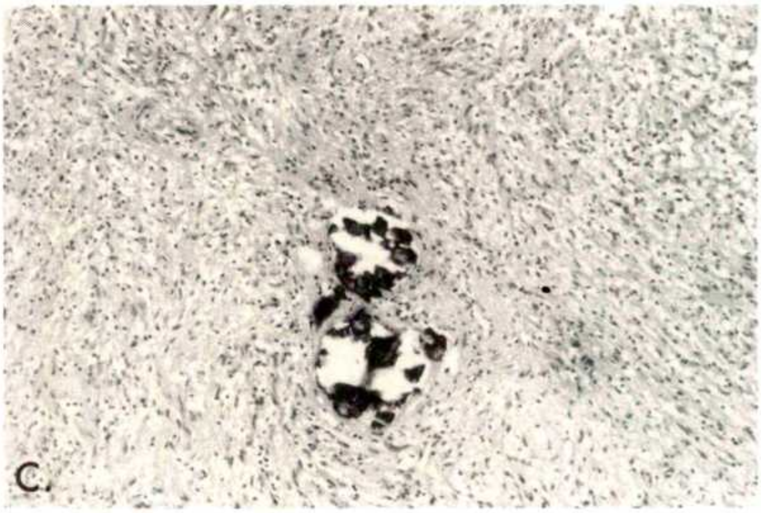

Fig. 13C *Case 1: Light microscopy of tumour from case 1 showing a basically Antoni B pattern with a central area of calcification. (H. and E., ×44).*

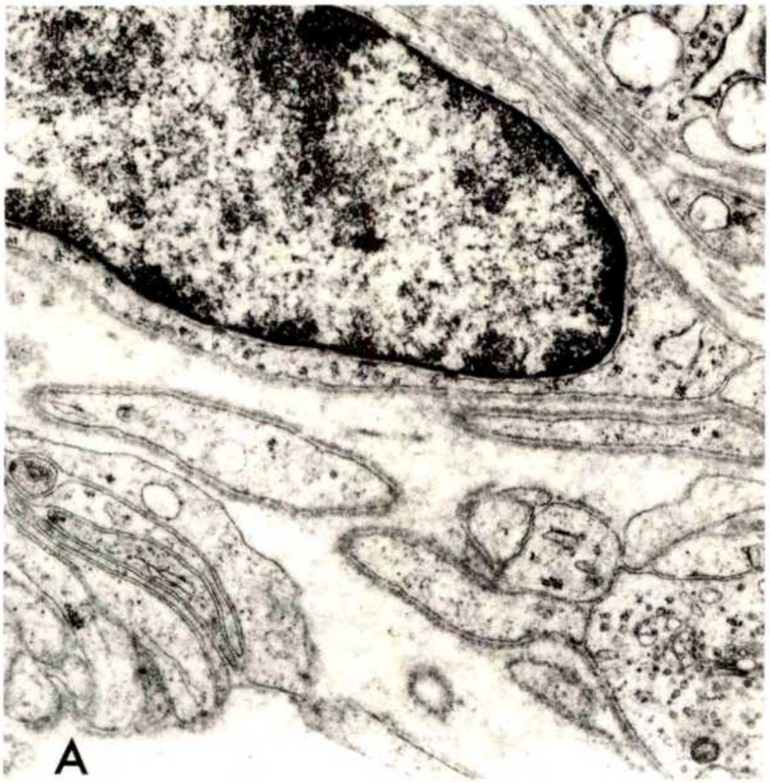

Fig. 14A *Case 3: Electron micrograph of tissue from case 3 showing Schwann cells with interdigitating and convoluted cell membranes with few subcellular organelles and a prominent extracellular basement membrane. (× 18 110).*

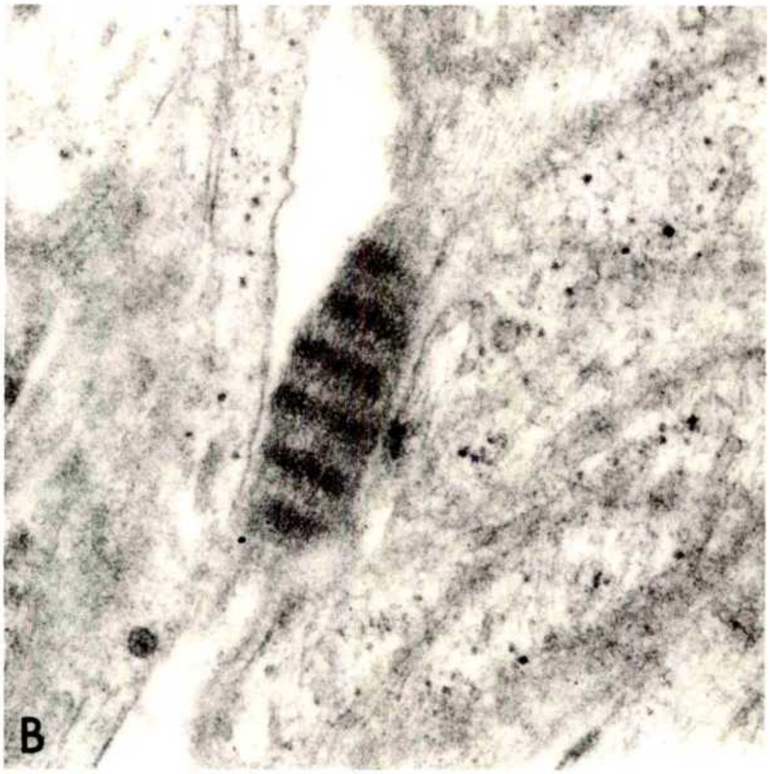

Fig. 14B *Electron micrograph from an intraconal schwannoma shown in Fig. 14A. This demonstrates 'long spacing' collagen adjacent to a cell membrane (× 50 700).*

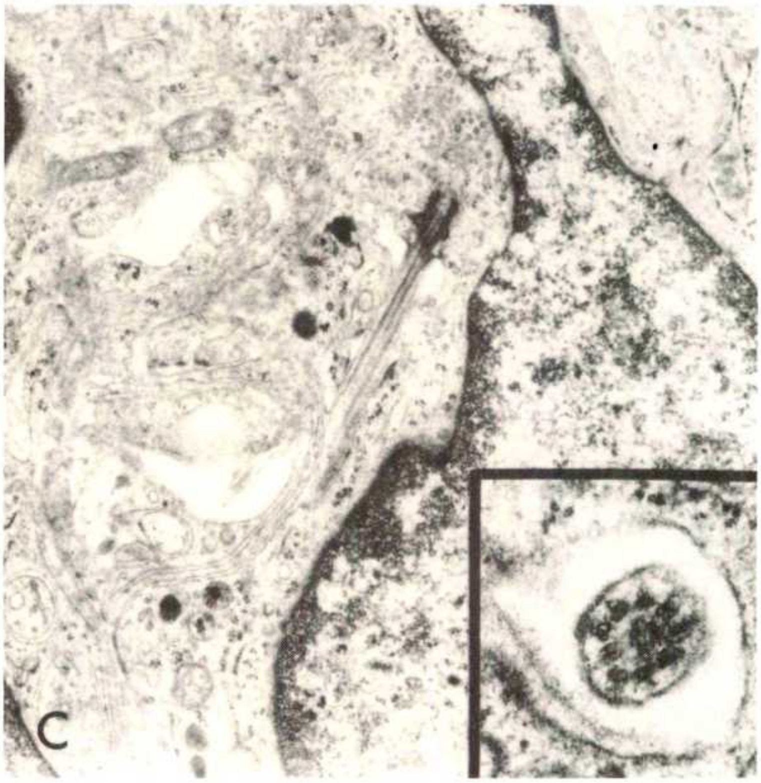

Fig. 14C *Case 2: Electron micrograph from the lesion described in case 2. Note adjacent to the nuclear membrane is a longitudinal section of a cilia (× 8500). Insert shows a cilium in cross section (× 66 000).*

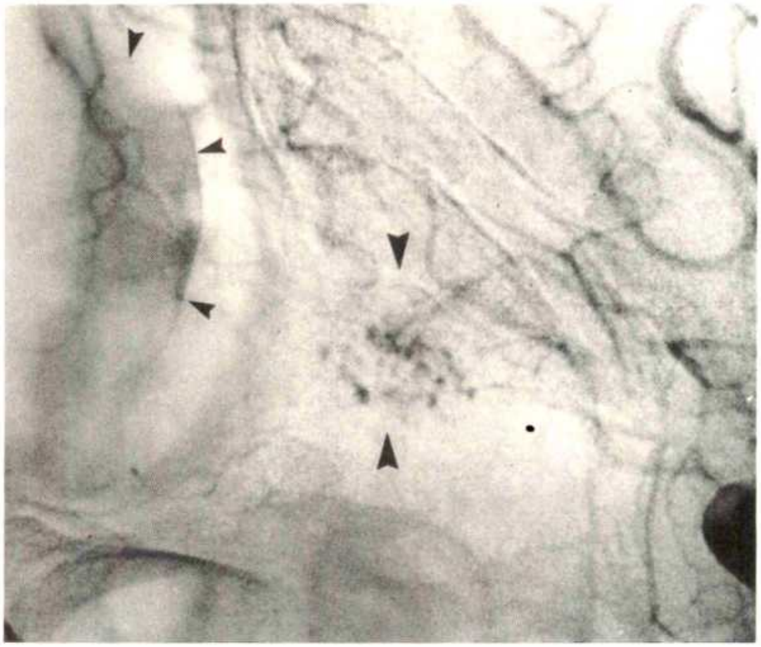

Fig. 15 *Carotid arteriogram, subtraction view, of histologically proved cavernous haemangioma showing late minor pooling of dye (between large arrowhead). Small arrowheads define the choroidal crescent.*

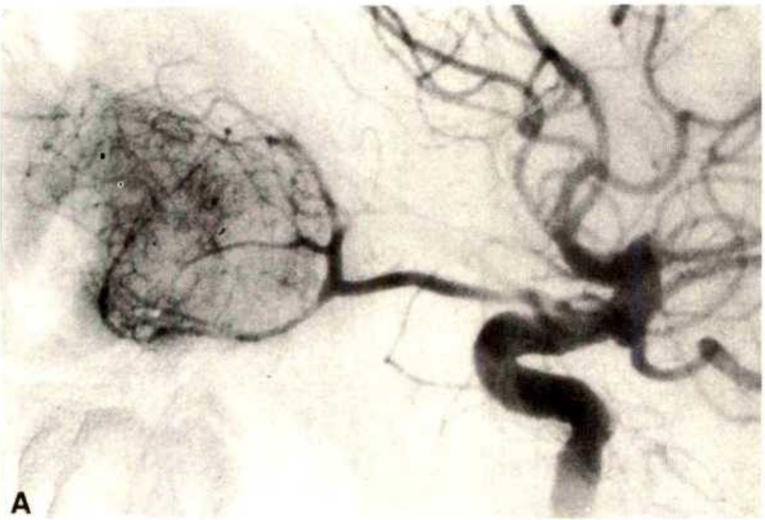

Fig. 16A *Early phase, carotid arteriogram, subtraction view, of histologically proved optic nerve meningioma demonstrating multiple tumour vessels.*

typical varicose, violaceous tumour vessels on their surface. Four nerves were specifically identified in association with their respective lesions, all of which were removed leaving the nerves of origin intact. The associated nerves were: superior division of the third, sixth, infraorbital, and superior division of the ophthalmic nerve.

Histology was variable but typical of schwannoma, including mixed Antoni type A and B patterns (Fig. 13A), tumour capsule, thick walled hyalinised vessels (Fig. 13B), perivascular lymphocytic cuffing, calcification (Fig. 13C), organoid arrangements of Schwann cells with Verocay bodies (Fig. 13B), loose collagenous stroma, and occasional nuclear pleomorphism. Electron microscopy confirmed the schwannian origin in each of the tumours (Fig. 14A). Long spaced collagen was identified in one of the tumours only (Fig. 14B). An unusual electron microscopic feature noted in one of the tumours was the presence of a typical cilia (Fig. 14C).

Discussion

Primary schwannoma rarely occurs in the orbit. Although no single feature is pathognomonic, a multiplicity of clinical, radiographic, and surgical features point to the diagnosis of this lesion. It is a disease primarily of adults, has an insidious onset, is slow growing, and is noninvasive with minimal effect on other orbital structures. The range of clinical

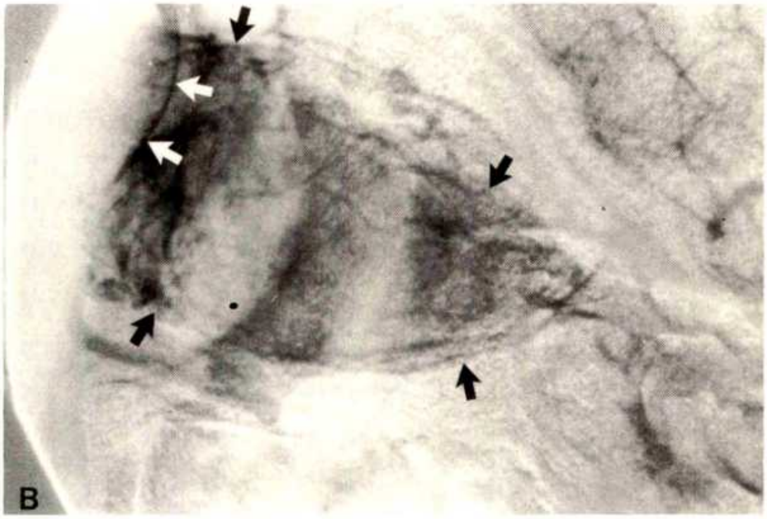

Fig. 16B *Same lesion, late phase, demonstrating tumour blush (black arrows); white arrows indicate choroidal crescent.*

presentation in our patients included optic neuropathy, proptosis, diplopia, anterior orbital mass, and sinusitis. Of available investigations CT scan was found to be the most useful, particularly in localising the lesion, whether within the orbit or extending into it from periorbital soft tissues or paranasal sinuses. The configuration varies from round to oval, and the tumour generally has a well-defined margin and, if intraconal, is well demarcated posteriorly. On CT scan most lesions enhanced to a mild degree, but on carotid arteriography there is no uptake of dye. Ultrasonography confirmed the presence of a discrete, encapsulated, solid-mass lesion. Other slow growing orbital tumours to be considered in the differential diagnosis are cavernous haemangioma, meningioma, and haemangiopericytoma. In our experience, on carotid arteriography, cavernous haemangiomas show late minor pooling of the dye (Fig. 15), while meningiomas have multiple tumour vessels and a late blush (Fig. 16A, B). Haemangiopericytomas have an early florid blush. These 3 lesions when compared with schwannomas showed more marked enhancement with contrast on CT scanning. In addition, on CT scanning schwannomas tend not to follow a muscle or mimic muscle enlargement as is seen in thyroid ophthalmopathy, nor do the lesions extend into and obscure the apex of the orbit, as may be seen in orbital pseudotumour or intrinsic optic nerve lesions.[4–7] Although previous series[8–11] all describe lesions of large size, a high index of suspicion, accurate localisation, and determination of size by the methods described here allow small, symptom-causing lesions to be treated early and successfully, as demonstrated in case 2. Primary orbital schwannomas are typically benign, encapsulated, noninvasive tumours. Thus surgical excision as a definitive therapy is indicated.

The surgical approach, whether anterior, lateral, or combined lateral-orbitotomy and frontal-craniotomy, was dictated by the location of the lesions as determined by preoperative investigations. Surgical removal may be total or subtotal, in piecemeal fashion, or by evacuation of the tumour from within its capsule. The type of removal is dictated by the location and attachments to adjacent structures. Because of the peripheral outpouching characteristic of schwannomas they may be successfully stripped of the nerve of origin by microscopic techniques. Like other authors, in a follow-up ranging from 6 months to 5 years we have had no recurrences.[8–10]

Histological examination also showed the variability of the tumours.[2,3] Antoni types A and B were found in addition to more fibrous types and some areas of cellular pleomorphism. Electron microscopy confirmed the Schwann cell origin in all cases and was typical of Schwann cell tumours previously described.[2] The unusual finding of cilia in one case is not a specific feature of schwannomas but has been described in many tumours of both epithelial and mesenchymal origin.[12]

In conclusion, primary orbital schwannomas are a rare orbital and periorbital tumour with variable anatomical and histological expressions. Preoperative differential diagnosis of a slow-growing soft tissue orbital or periorbital mass includes schwannoma. Although CT scan is helpful in localising and identifying the lesion, no single pathognomonic investigative procedure or feature exists. Rather a constellation of features point to this diagnosis. Surgical excision is indicated and to date has been successful.

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Use in children
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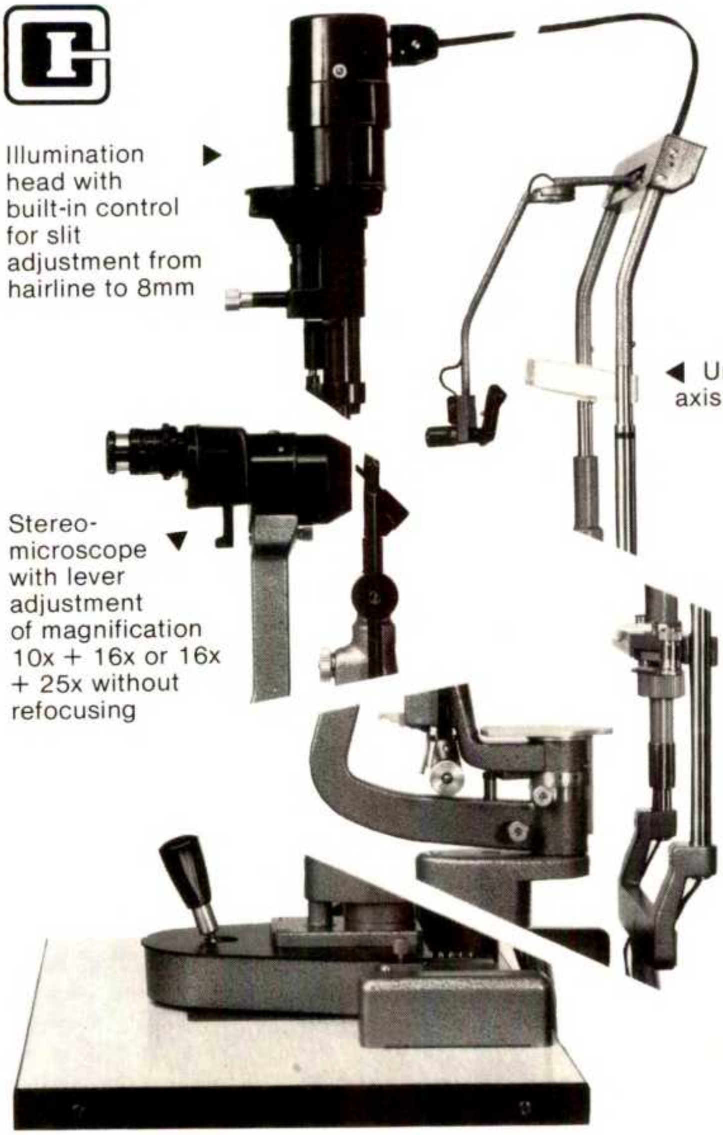

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British Journal of Ophthalmology, 1982, **66**, 205–208

Fulminating panophthalmitis due to exogenous infection with *Bacillus cereus*: report of 4 cases

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SUMMARY *Bacillus cereus* is a seldom recognised but important cause of panophthalmitis. Although most reported cases have been the result of endogenous infection, we have recently seen 4 cases that followed ocular trauma. In each instance a fulminating panophthalmitis developed, accompanied by fever and leucocytosis. Despite prompt therapy all eyes were rapidly lost. In view of the selective antibiotic sensitivities of this organism and the fulminating course of the disease, conventional approaches to therapy, including standard prophylactic antibiotic regimens, are unlikely to be successful in such cases. Analysis of our cases suggest that ocular infection with *B. cereus* has certain features that may allow a provisional diagnosis to be made before isolation of the organism. Early recognition and prompt institution of effective therapy may lead to salvage of these eyes in the future.

Bacillus cereus is an unusual ocular pathogen. Haematogenous dissemination, usually in drug abusers, has been the route of infection in almost every reported case.[1-5] Only 2 instances of exogenous infection have been reported in the past 30 years.[5 6] However, we believe the reports may not accurately reflect the incidence of exogenous infection by this microorganism. During 1976–9 we treated 4 cases of traumatic panophthalmitis caused by *B. cereus*.

Case reports

CASE 1

A 33-year-old healthy Caucasian farmer presented to the Vanderbilt University Eye Clinic in severe ocular pain. Seventeen hours earlier a piece of metal entered his right eye while he was striking a metal cornpicker with a hammer. Vision was reduced to light perception, the lids were swollen and ecchymotic, and the conjunctiva was severely chemotic. On slit-lamp examination the cornea was diffusely oedematous, with both iris and vitreous prolapsing through a 2 mm scleral wound adjacent to the limbus. The anterior chamber was flat, and fundus details could not be visualised. A foreign body was localised outside the globe by radiography. Although the patient was afebrile, his white cell count was 14×10⁹/l. Antibiotic therapy with intravenous gentamicin (3 mg/kg/day) and methicillin (80 mg/ kg/day) was begun. After excision of the prolapsed tissue the wound was repaired. 20 mg of gentamicin and 40 mg of dexamethasone were injected subconjunctivally.

Postoperatively the patient denied light perception in the injured eye. He became febrile (100·4°F, 38°C). The eye was markedly proptosed and a peripheral corneal ring abscess had developed. Large Gram-positive rods and Gram-positive cocci were seen in a Gram stain from a conjunctival smear, raising the possibility of a clostridial infection. Fortified gentamicin (13·5 mg/ml) and 'fortified' bacitracin (10 000 U/ml) were given topically every hour, and aqueous penicillin (250 000 U/kg/day) together with gentamicin and methicillin were administered intravenously daily. However, worsening proptosis and extreme pain necessitated evisceration 12 hours later. Therapy was continued 4 more days, and the patient recovered uneventfully. *Bacillus cereus* was isolated from prolapsed tissue and cornea at the time of the initial operation and from the ocular contents removed at evisceration. Cultures from the corneal wound and prolapsed tissue also yielded enterococci.

CASE 2

A 43-year-old Caucasian labourer was hammering an axe head in his barn when a metal fragment entered

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his left eye. Twenty-four hours later he presented to Vanderbilt University Eye Clinic with a severe proptosis and conjunctival chemosis. A peripheral ring of oedema was visible in the cornea of the injured eye. Computerised axial tomography (CT scan) revealed the presence of a metallic intraocular foreign body in the posterior sclera of the left eye, but it could not be seen owing to the presence of massive vitreous haemorrhage. Although he was afebrile his white cell count was 16×10^9/l. Vision was reduced to light perception. Intravenous therapy with gentamicin (4 mg/kg/day) and methicillin (80 mg/kg/day) was begun. At surgery prolapsed retina and vitreous were excised. The foreign body was extracted through the entry wound 7 mm posterior to the superior limbus, and 250 μg of gentamicin was injected into the vitreous cavity. During the operation the surgeon observed the rapid development of a ring-shaped abscess in the area of the previously noted corneal oedema.

Postoperatively the patient's temperature rose to 100·4°F (38°C). He was unable to perceive light. Proptosis became extreme and the abscess spread to involve the entire cornea. A culture of the scleral wound taken at surgery yielded *Bacillus* sp. and a coagulase negative staphylococcus. Intravenous antibiotic therapy with gentamicin and methicillin was continued, but 24 hours after the primary wound repair the eye was eviscerated because of severe pain. Intravenous chloramphenicol (50 mg/kg/day) was given postoperatively for 5 days. The patient became afebrile within 24 hours, and his white cell count returned to normal. *Bacillus cereus* was isolated from the eviscerated ocular contents.

CASE 3

A piece of metal entered the left eye of a healthy 6-year-old boy watching his father strike a hatchet with a hammer in the workshop of their farm. The next day, when he presented to the eye clinic at Vanderbilt Hospital, he had a fever of 100·8°F (38·2°C) and a white cell count of $24{\cdot}5\times10^9$/l. He was in severe pain and vision was reduced to light perception in the injured eye. The conjunctiva was chemotic and a ring infiltrate was present in the peripheral cornea. The fundus could not be seen owing to the presence of a large blood-stained hypopyon. Radiography of the left orbit revealed a metallic foreign body within the eye. After conjunctival cultures were taken, intravenous gentamicin (5 mg/kg/day) and methicillin (100 mg/kg/day) were begun. Approximately 40 hours after the injury a large magnetic foreign body was removed through the scleral laceration 6 mm posterior to the limbus. After debridement of prolapsed necrotic retina and vitreous the wound was closed and a Silastic sponge was sewn into place. Gram-positive rods were seen in a smear of the excised retina and vitreous. Since infection with *Clostridium perfringens* was possible, intravenous penicillin (250000 U/kg/day) was administered postoperatively in addition to the other antibiotics. 'Fortified' bacitracin (10000 U/ml) and 'fortified' gentamicin (13·6 mg/ml) were given topically every hour.

Postoperatively the eye was blind. Proptosis worsened markedly with conjunctiva prolapsing through the lids. The cornea was totally opaque and necrotic. Twenty-four hours after surgery, because of increasingly severe pain, the eye was eviscerated. Intravenous antibiotic therapy, with the addition of chloramphenicol (50 mg/kg/day), was continued for 5 days, and the patient recovered uneventfully. *Bacillus cereus* was isolated in pure culture from the eviscerated ocular contents. Conjunctival cultures taken at the time of initial examination, and cultures of the scleral wound taken at the time of primary repair, revealed a heavy growth of *B. cereus*.

CASE 4

A 28-year-old plumber was hit in the right eye by a piece of metal while he was hammering a steel bolt. He was in severe pain, and the visual acuity in the injured eye was reduced to 6/60 when he presented to the eye clinic 7 hours after the injury. The cornea appeared normal, but the sclera was lacerated superiorly 3 mm from the limbus, with iris and vitreous prolapse. A moderate cellular reaction was present in the anterior chamber, and the pupil was peaked superiorly. He was afebrile and had a normal white cell count. An intraocular foreign body was demonstrated by radiography. Therapy with intravenous gentamicin (5 mg/kg/day) and methicillin (100 mg/kg/day) was immediatey begun. Three hours later, after an unsuccessful attempt at removal of a foreign body, the prolapsed tissue was excised and the laceration repaired. Intravenous antibiotics were continued postoperatively.

About 36 hours after surgery his temperature rose to 100·8°F (38·2°C) and his white cell count was 19×10^9/l. The eye was blind and he was in severe pain. A ring abscess had developed in the peripheral cornea. Ten hours later lid swelling and proptosis of the right globe became so severe that a lateral canthotomy was necessary. Fifty-eight hours after the injury the eye was eviscerated. Intravenous chloramphenicol (60 mg/kg/day) was given with gentamicin for 5 days postoperatively and recovery was uneventful. *Bacillus cereus* was isolated from the intraocular contents. The wound cultures taken at the time of primary repair yielded *B. cereus* and a coagulase-negative staphylococcus.

LABORATORY STUDIES

Bacillus cereus was isolated separately from eviscerated ocular contents and the entry wound in all 4 cases, from one extracted foreign body, and from the conjunctiva at the time of presentation in one case. In 3 patients a second organism was also present: coagulase-negative staphylococcus in 2 eyes and enterococcus in a third. Each *Bacillus* sp. was initially identified by Gram stain morphology, with final differentiation by biochemical testing. All isolates were resistant to penicillin, the semisynthetic penicillins, and the cephalosporins but sensitive to gentamicin, clindamycin, vancomycin, and chloramphenicol by the Kirby-Bauer disc diffusion method for in-vitro susceptibility testing.

Discussion

The aerobic Gram-positive bacilli are large endospore- forming rods. Until recently these micro-organisms, with the exception of *Bacillus anthracis*, have been considered to be only mildly pathogenic for man. However, their involvement in a number of serious infections, including bacteraemia, endocarditis, meningitis, and food poisoning is now accepted.[4 7-10] Since 1890 many cases of panophthalmitis attributed to *Bacillus* sp. have been recorded,[11] and in 1934 François emphasised the destructive nature of *Bacillus* infection in a paper reporting 41 cases that followed trauma.[12] Because of uncertainty over classification of this group of micro-organisms, precise identification of isolates was seldom successful. In 1952 Davenport and Smith[6] described the first culture-proved case of panophthalmitis caused by *B. cereus*, and since then the importance of this micro-organism in blood-borne infections has been emphasised in a number of papers.[1-5] However, only 2 cases of exogenous ocular infection have been reported; both followed penetrating trauma.[5 6]

The clinical features of all our cases were remarkably similar. Three of the injuries occurred in an agricultural or rural setting; the fourth patient was at home using a hammer on a metal bolt. The low-velocity metallic projectiles entered the eye at the limbus or anterior sclera, causing prolapse of vitreous into the conjunctival sac. Three foreign bodies were retained with the eyes; the fourth had its exit through the posterior sclera. Except for one patient who was examined within 7 hours of the injury, vision was reduced to light perception at the time of presentation. Subsequently vision in all eyes deteriorated rapidly to no light perception. Initially the severity of reactive orbital cellulitis, as indicated by proptosis, lid swelling, and loss of ocular movement, was variable. As the infection advanced, however, these signs dominated the clinical picture and in one case were extreme enough to require emergency canthotomy.

Progressive corneal changes appear to be a feature of this infection. Characteristically a ring of oedema adjacent to the limbus developed 24 to 36 hours after the injury. Within another few hours this area became infiltrated with inflammatory cells, and by 30 to 60 hours a ring abscess was evident. This distinctive finding has also been reported in endogenous cases.[2 3 5]

Standard management of the injuries proved to be ineffective. Despite debridement, closure of the entry wounds, foreign body removal, and comprehensive antibiotic therapy the infections progressed inexorably, accompanied by fever and a moderate leucocytosis. Evisceration was necessary within 2 to 3 days of the injury, and thereafter the systemic reaction abated promptly. In each case infection with *B. cereus* was confirmed by recovery of the micro-organism from the eviscerated ocular contents; in 3 cases a second organism was also present.

Bacillus species are present in air, soil, water, milk, dust, wool, and faeces. Since the injuries in all cases occurred in a setting where these micro-organisms could have contaminated the tools being used, it is likely that the low-velocity foreign bodies carried bacteria into the eye. However, this explanation may not apply to all cases. Although penetrating injuries due to low-velocity projectiles are frequent, this devastating infection occurs only rarely, suggesting that other mechanisms need to be considered. In each of our cases vitreous prolapse was present and may have provided a portal of entry for organisms already present in the conjunctiva. Although *B. cereus* is not a usual inhabitant of the conjunctival sac, Van Bijsterveld and Richards[13] showed that it may become part of the flora in the appropriate environment. They isolated *B. cereus* from 40 eyes of asymptomatic, infection-free individuals engaged in the processing and handling of hay or the care of stables and horses at a race track. It is therefore of interest that *B. cereus* was recovered from the conjunctiva of one of our patients (case 3) at the initial examination.

Once the micro-organism gains access to the vitreous, infection appears to progress with remarkable speed. It is evident that panophthalmitis is established within 48 hours of injury. This unusually fulminating course appears to be characteristic of *B. cereus* infection and distinguishes this micro-organism from the other Gram-positive aerobic bacilli. While it is not clear why *B. cereus* should be so devastating to the eye, it seems likely that exotoxin production plays a part.[9] *Bacillus cereus* is known to elaborate a number of exotoxins, including phospholipase C, haemolysin, several proteases, and an enterotoxin.[14] Although the ocular effects of these metabolites have yet to be investigated, each has the potential to inflict direct tissue damage. The enterotoxin, which has both dermonecrotic and vascular permeability effects, has been shown to be the cause of diarrhoea in *B. cereus* food poisoning.[15]

The loss of every eye infected with *B. cereus* reported thus far highlights the limitations of present therapeutic approaches. The isolates from our cases were resistant to natural penicillins, the semisynthetic penicillins, and the cephalosporins. They were susceptible to gentamicin, one of the antibiotics routinely used following penetrating ocular trauma. The inability of gentamicin to control the infection in our cases illustrates the need to develop fresh approaches to treatment. Studies in our laboratory are now in progress evaluating several other antibiotics, including clindamycin and vancomycin. Clindamycin alone or in combination with other antibiotics may prove to be a useful antibiotic for treatment of this infection in view of its excellent ocular penetration.[16]

This work was supported in part by NIH grant EY 01621 and an unrestricted grant from Prevention of Blindness, Inc.

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Acute anterior uveitis after yersinia infection

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SUMMARY Twenty-eight cases of acute anterior uveitis in which raised antibody titres indicated yersinia infection as a possible causative factor in the disease were studied retrospectively. In most cases the antibodies belonged to the IgA class; in only 6 patients did the presence of IgM class antibodies indicate recent infection. In half the cases also antibody titres against *Chlamydia* were raised. The clinical features and course of the disease did not differ from those of acute anterior uveitis due to other causes.

Acute anterior uveitis (AAU) is a common disease usually affecting young or middle-aged patients. It frequently occurs in connection with other disorders such as Reiter's disease, ankylosing spondylitis, juvenile rheumatoid arthritis, psoriatic arthritis, and sarcoidosis. It may also follow certain infections—for example, by *Chlamydia trachomatis*, salmonella, or yersinia—as a late complication.[1–3] It is noteworthy that AAU and several of the other disorders mentioned above are correlated with the presence of HLA B27.[4–6] This has also been demonstrated for the reactive arthritis that develops after acute enteritis caused by yersinia.[7–9]

AAU related to yersinia infection has not been earlier studied as a separate entity. For instance, it is not known how frequently yersinia infection is the cause of AAU and whether these cases are characterised by special clinical and immunological features. The purpose of the present work was to elucidate these questions by analysing retrospectively 28 cases of AAU in which elevated antibody titres indicated yersinia infection as a possible causative factor in the disease. We have studied the ocular pathology, the rate of recurrence, and the overall prognosis of these cases, and paid special attention to the presence of certain clinical features, such as diarrhoea and arthritis.

Patients and methods

The subjects of the study were 15 women and 13 men with AAU who had significant amounts of anti-yersinia antibodies in their sera. They were examined at the outpatient department of the Clinic for Ophthalmology at Turku University from March 1979 to September 1980. Patients who had AAU due to ocular trauma were excluded from the study.

The diagnosis of AAU was in all cases confirmed by biomicroscopic examination. The following laboratory tests were carried out on each patient: erythrocyte sedimentation rate (ESR), peripheral blood leucocyte count, the latex and Waaler-Rose test for rheumatoid factor, antistreptolysin O, antistaphylolysin, anti-yersinia-antibody, and anti-chlamydia antibody determinations, and *x*-ray examination of the chest, sinuses, and lumbosacral spine. The hospital records were reviewed with attention to the severity of the AAU and its course as well as possible recurrences and associated diseases.

The ELISA method (enzyme-linked immunosorbent assay) for IgM, IgG, and IgA class yersinia antibodies has been described in detail previously.[10] In brief, the assay was a double antibody utilising immunoglobulin class-specific rabbit antihuman sera and swine antirabbit IgG alkaline phosphatase conjugate. The antigen preparations used were formalinised whole *Y. enterocolitica* 0:3 and *Y. pseudotuberculosis* IA bacteria[11] and heat-treated (100°C for 1 h) *Y. enterocolitica* 0:9 bacteria. The results were evaluated by means of a standard curve constructed from measurements on 6 different dilutions of serum with a high concentration of the corresponding antibody to yersinia. The results are presented as percentage values of the standard serum.

Results

Of the 28 patients included in the study 15 (54%) were women and 13 (46%) were men; AAU is known

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to affect both sexes equally. The patients represent primarily young and middle-aged people, the mean age being 38. The youngest patient was 17 and the oldest 65 years old. The mean age of the women was 36 years (range 23–64) and of men 43 years (range 17–65 years).

The AAU was bilateral in 6 patients. In 9 cases (32%) there had previously been AAU. The ocular pathology and the duration of the symptoms in patients who had raised anti-yersinia antibodies did not differ from the other cases of AAU treated at the same time in the Clinic for Ophthalmology. In no case was a relapse observed during the relatively short follow-up period. In only one patient was the disease so severe that systemic steroid treatment was given. All others were treated by topical mydriatics and corticosteroids. Three patients received tetracycline because of fresh arthritis and/or diarrhoea. The one patient who had systemic corticosteroid therapy received tetracycline.

The results of the laboratory tests are presented in Table 1. It is remarkable that none of the patients had a positive latex test for rheumatoid factor and only one had a positive Waaler-Rose test. The ESR remained low in most patients, and only in 2 cases was it over 40 mm/h. The other laboratory tests did not reveal any significant changes typical of AAU. In 3 patients ankylosing spondylitis was also diagnosed at this time; its duration could not be established with certainty.

The clinical features of interest in the patients are summarised in Table 2. The raised yersinia antibodies belonged in most cases to the IgA class, and only in 6 patients were the IgM antibodies raised, indicating a recent infection by yersinia. In most cases the antibodies were against *Y. enterocolitica* 3, in 4 against *Y. enterocolitica* 9, and in 3 patients against *Y. pseudotuberculosis* IA. Five patients (17·9%) had had diarrhoea in the initial phase, and in 3 cases (10·7%) the patient had reactive arthritis. One of those 3 patients also had raised antibodies against chlamydia in a titre of 1:32.

In 7 cases high antibody titres ≥1:32 against chlamydia were observed; this represents 25% of the whole material (Table 1). A further 7 patients had lower anti-chlamydia antibody titres of ≥1:16. Taken together, 50% of the patients thus had raised antibody titres both against yersinia and chlamydia. The question therefore arose whether these 2 agents have cross-reacting or common antigens or whether the patient had 2 infections simultaneously. The 7 sera with high antibody levels against both agents were absorbed with yersinia; in 6 cases the absorption caused no drop in the anti-chlamydia titres. One serum lost its anti-chlamydia titre of 1:128 when absorbed with yersinia. This serum is being studied further to find out whether the antibody is truly cross-reactive. Anyway it is apparent that generally the appearance of antibodies against both yersinia and chlamydia indicates double infection.

Table 1 *Number of positive laboratory findings in 28 patients with AAU after yersinia infection*

ESR >40	2 (7·1%)
Leucocytes $>10\times10^9$/l	3 (10·7%)
Latex + + — + + +	0
Waaler-Rose ≥ 256	1
AST titre >400	0
Serological test for chlamydia ≥ 32	7 (25·0%)
Serological test for chlamydia ≥ 16	14 (50·0%)

Table 2 *Clinical features and anti-yersinia antibodies in 28 patients with AAU after yersinia infection*

Patient	*Age*	*Sex*	*Diarrhoea*	*Arthritis*	*Yersinia antibodies %*		
					IgG	*IgM*	*IgA*
1	52	M	–	–	—	—	38
2	68	M	–	–	—	—	>500
3	68	M	–	–	—	—	58
4	29	F	–	–	10	—	64
5	27	F	–	–	18	62	>500
6	33	F	–	+	—	—	14
7	48	F	–	–	—	—	25
8	19	M	+	–	198	100	>500
9	44	F	+	–	—	—	32
10	32	F	+	+	14	—	161
11	63	M	–	–	16	—	38
12	25	M	–	–	—	—	8
13	38	M	–	–	—	—	14
14	50	M	–	–	10	—	41
15	23	M	–	–	—	—	17
16	57	M	–	–	—	—	12
17	36	M	–	–	—	—	37
18	45	M	+	–	68	—	134
19	31	F	+	+	8	86	41
20	52	F	–	–	—	—	26
21	55	F	–	–	9	29	31
22	35	F	–	–	10	—	37
23	36	F	–	–	30	—	—
24	40	F	–	–	—	—	13
25	32	F	–	–	—	—	27
26	24	F	–	–	—	35	10
27	46	M	–	–	—	29	65
28	28	F	–	–	146	—	—

Discussion

Our observations indicate that AAU after yersinia infection does not clinically differ from that caused by other aetiological factors. Only 5 patients had had diarrhoea that suggested the possibility of yersinia as primary cause of the disease. This is in concordance with the clinical observation that, in patients who later develop arthritis, diarrhoea is not a prominent initial symptom.[12] The general symptoms were mostly mild. The ESR was low, and only 2 patients had a value higher than 40 mm/h, whereas in yersinia arthritis the ESR value is usually high.[13 14] Only one of the patients (case 10) had severe general disease. She had originally a yersinia enteritis with diarrhoea, followed by severe arthritis. At this time she was bedridden for several weeks with synovitis in many joints and extensive muscular atrophies. She recovered well, however, and had a successful pregnancy after this. Throughout this time the antibody titres of the IgA class remained high. Stool cultures did not yield yersinia. After the delivery she developed AAU but recovered well from this also. Then, suddenly and surprisingly, the antibodies disappeared, and at present she is clinically quite healthy.

Only in 3 cases did the patient also have arthritis. This suggests that these 2 complications of yersinia infection can hardly have a common pathogenic pathway. Only in 6 patients was the AAU bilateral. Interestingly, relapsing AAU is not restricted to the same eye but may affect one or the other. It seems therefore that some unknown factor is needed to trigger the inflammatory process in the eye.

In 26 of the 28 cases the IgA class antibodies against yersinia were raised and only in 12 cases were high levels of IgG class antibodies observed. Of these, 2 had the IgG antibodies as the only class present in their sera. In 6 patients high IgM class antibodies indicated that the yersinia infection had been recent. The observation is in accordance with the findings that in yersinia arthritis the IgA class antibodies are high and remain elevated for prolonged periods even after the actual joint symptoms have disappeared.[9 15 16] The reason for this phenomenon remains unclear, and persistence of the antigen in the organism, for example, has not been demonstrated. In any case it is obvious that high IgA anti-yersinia antibodies are correlated with the occurrence of postinfectious complications, although their role remains obscure.

The present material indicates that yersinia infection as a cause of postinfectious AAU is far less common than chlamydia infection. In the present series as many as 14 (50%) patients had anti-chlamydia antibodies, 7 (25%) of these at a high level. The same high incidence of anti-chlamydia antibodies has been observed also in another follow-up study in our clinic,[1] whereas out of 121 consecutive cases of AAU only 13 (10·7%) could be considered as caused by yersinia. Moreover, 3 patients in our material had as an underlying disease ankylosing spondylitis, to which AAU is known to be correlated. The absorption studies of the sera show that at least in 6 out of the 7 cases studied the patient had both chlamydia and yersinia infection simultaneously. It is not possible to conclude whether one of the 2 or both infections together caused the AAU.

A practical problem related both to the arthritis and AAU after yersinia infection is the possible need of antibiotic treatment. It seems that in both diseases[13 14 17] the bacteria disappear quickly from the stools and the diagnosis has to be based on the demonstration of antibodies; in our material stool cultures were not carried out. The same holds true also for chlamydia, which can rarely be isolated at the time of diagnosis of AAU.[1] In the present study 4 patients received tetracyclines and the others were treated only with topical mydriatics and steroids. All recovered well. It seems reasonable to apply antibiotic therapy only in the cases where high levels of IgM antibodies indicate recent infection, when yersinia can be cultured from the stool, or when diarrhoea and abdominal pains are still present or closely connected with the illness.

In conclusion, AAU may be frequently related to yersinia infection. The clinical disease does not differ from that caused by other aetiological factors, such as chlamydia, and is not connected with the occurrence of other late complications of yersinia infection such as erythema nodosum or reactive arthritis. Although immunological mechanisms are a major factor in the pathogenesis of the different postinfectious complications, their actual role and character still remain obscure. Apparently some local factors are necessary to trigger the final inflammatory process in the eye.

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Notes

Contact lens fitting

The Rudolph Ellender Medical Foundation Inc. will hold the 22nd annual instructional course in contact lens fitting on 1-4 April 1982 at New Orleans, Louisiana, USA. Details from Jos. A. Baldone, MD, President, 136 South Roman Street, New Orleans, LA, USA.

Centenary of Sydney Eye Hospital: International Scientific Meeting

An international scientific meeting celebrating the centenary of Sydney Eye Hospital will be held on 3–7 April 1982. The venue is the Sydney Hilton Hotel, Level 9, 259 Pitt Street, Sydney 2001, Australia, to which registrants are advised to make their bookings direct, indicating that they are part of the conference. The theme of the meeting is 'Current concepts in ophthalmology' and emphasises management. Keynote lectures will be given in plenary sessions at the beginning of each morning and afternoon. These will be followed by a choice of symposia chaired by the overseas visitors who will give position papers allowing time for discussion. Inquiries about registration to Miss A. Fitzgerald, c/o The University of Sydney, Department of Clinical Ophthalmology, Sydney Eye Hospital, Sir John Young Crescent, Woolloomooloo, New South Wales 2011, Australia.

Clinical vision research

A course on 'Clinical vision research: epidemiologic and biostatistical approaches' will be held 29 April to 1 May 1982 in Sarasota, Florida (immediately before the 1982 ARVO meetings). The course is an introduction to contemporary methods and principles of clinical vision research, and is sponsored by the National Eye Institute and Epistat Associates. Further information from Catherine M. Beinhauer, Epistat Associates, PO Box 214, Norwich, Vermont 05055, USA.

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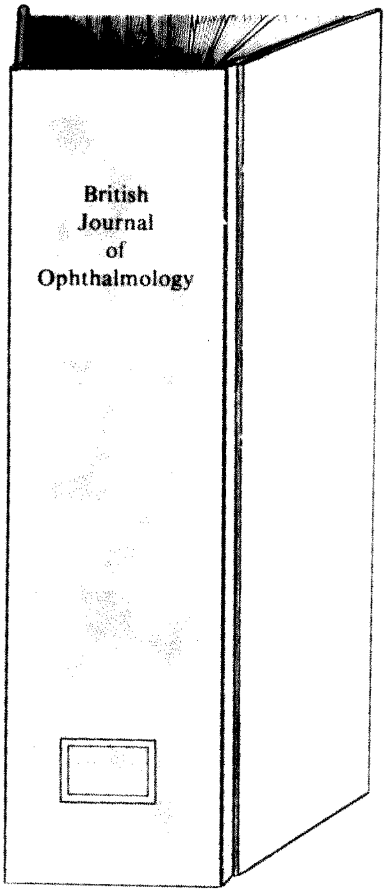

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ASTM CODEN BJOPAL 66 (3) 149-212 (1982)

ISSN 0007-1161

British Medical Association Tavistock Square London WC1H 9JR

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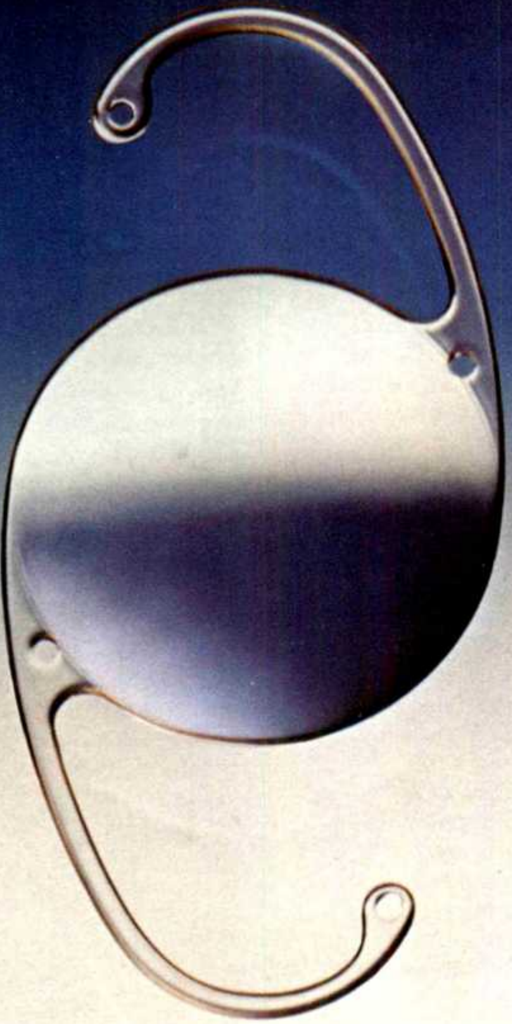

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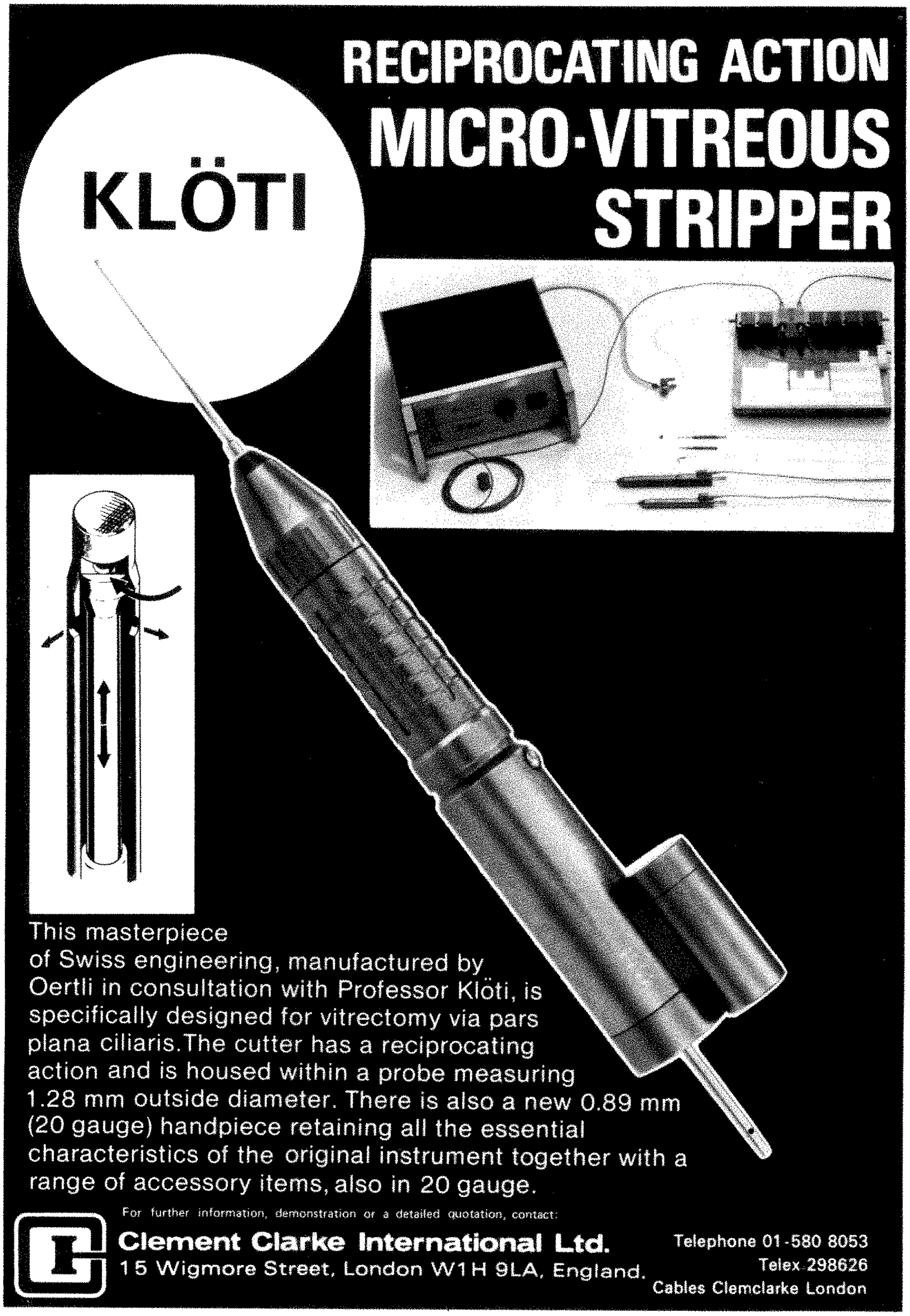

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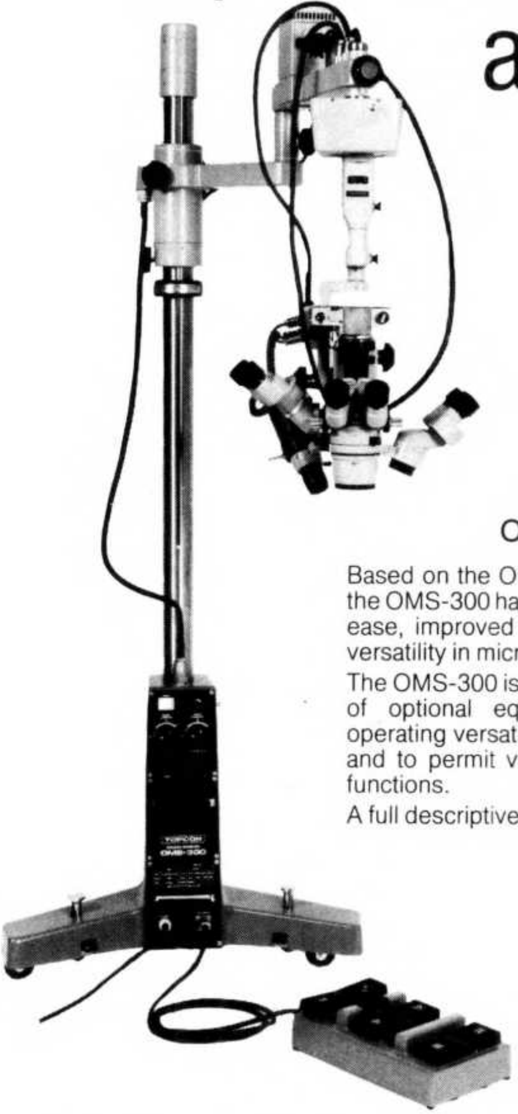

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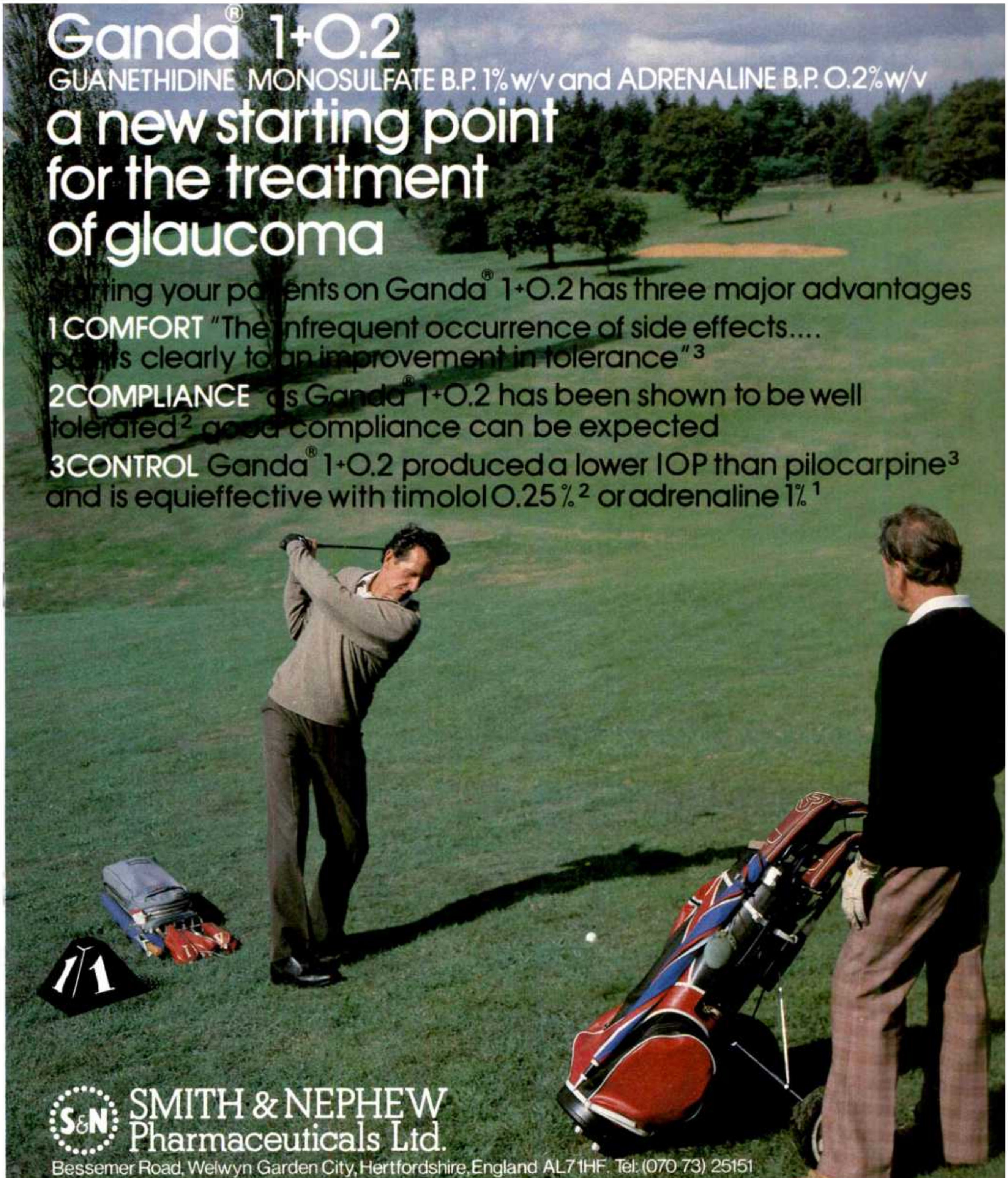

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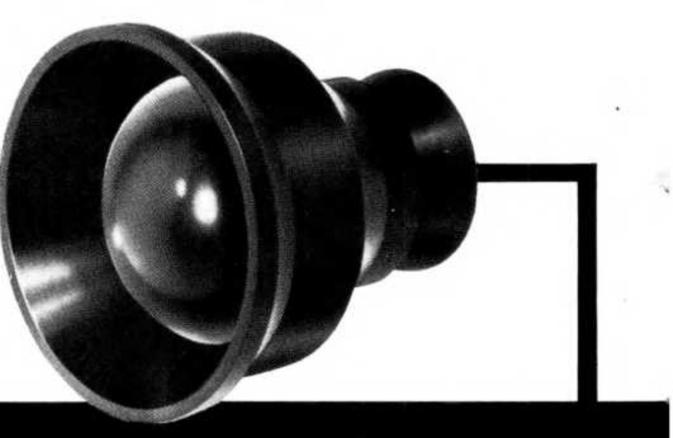

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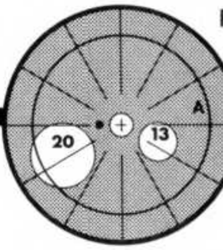

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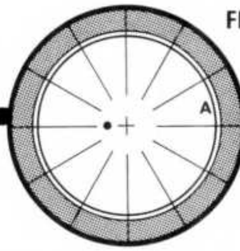

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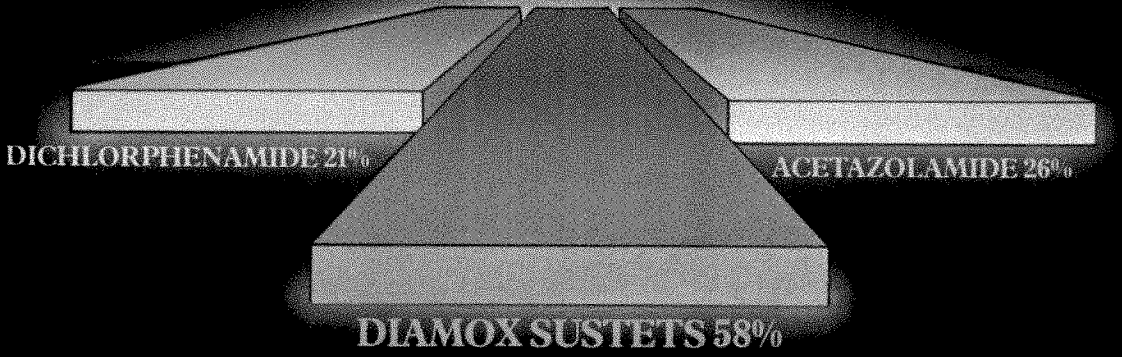

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A comparative trial of xenon arc and argon laser photocoagulation in the treatment of proliferative diabetic retinopathy

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SUMMARY We present the results of a randomised study comparing xenon arc and argon laser photocoagulation in the treatment of proliferative diabetic retinopathy. Our results show that when used in the way described below there is no significant difference between the effect of the 2 treatments on optic disc neovascularisation and visual acuity. We also compare the results of peripheral retinal ablation with those of panphotocoagulation in the argon and xenon groups. The results suggest that in some patients peripheral treatment may be sufficient to cause regression of disc neovascularisation.

Retinal photocoagulation was introduced by Meyer-Schwickerath but was used initially with little effect on diabetic retinopathy.[1] The first functioning laser was introduced by Maiman[2] and used to treat the eye by Zanet *et al.*[3 4] and Koester *et al.*[5] Initially the ruby laser was used to treat retinal lesions, but this was superseded by the argon laser[6] and used by Zweng to treat diabetic retinopathy.[7] Panphotocoagulation was first described by Aiello[8] using the ruby laser.

There have been 4 previous studies comparing the effects of argon laser and xenon arc photocoagulation. Fankhauser *et al.*[9] used long-duration argon treatment (0·25–1·5 s) and found little difference between argon and xenon. McLean[10] compared the side effects of the 2 treatments and found a higher incidence of field loss with xenon, but did not comment on the relative effectiveness of the 2 treatments.

The Diabetic Retinopathy Research Group in America[11 12] conducted a multicentre controlled trial on 1727 patients, randomly allocating one eye to the treatment group and one eye as control. The patient was then randomly allocated to an argon or xenon treatment group. The study showed a greater incidence of field loss and visual acuity loss with xenon. In the later report they showed a greater treatment effect with xenon at 2 and 3 years. However, they were unable to apply the standard statistical methods because of multiple response variables in several subgroups, making exact p values impossible to obtain. But the results did suggest that there was an early increased reduction of visual acuity with xenon in comparison with argon and the control group (in the first 6 weeks), and at a later stage loss of visual acuity was higher in the untreated group, with fewer patients having visual acuities of less than 5/200 in the xenon than the argon groups. Crick *et al.*[13] compared the effects of the 2 treatments on visual function in a total of 26 eyes and also the patients' preference. Xenon arc had a greater adverse effect on the peripheral field, and small reductions in visual acuity were more common with xenon. However, the effect on central fields, colour vision, and macular threshold was essentially the same. The difference in the effect of treatment on the prognosis of proliferative retinopathy and the extent of the side effects is presumably related to the extent of retinal damage caused by the 2 treatments.

Wallow and Davis[14] compared the post-mortem appearance of argon and xenon burns, and demonstrated that much deeper burns were caused by xenon arc. Two-thirds thinning of the retina was seen with all xenon burns, whereas this was seen only in argon treatment of longer duration (0·5 s). Other studies of interest include a 3-year study of peripheral retinal ablation with argon,[15] which showed a significantly better response for visual acuity in treated eyes. In 1977 a multicentre randomised controlled trial on the effect of xenon arc photocoagulation[16] showed a greater deterioration in the untreated eye at

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1, 2, and 3 years after treatment when patients had disc neovascularisation, but there was no significant difference if only peripheral new vessels were present. There was a greater response in the treated than untreated eyes. Oosterhuis[17] reported the results of a carefully designed trial of the effects of focal retinal treatment with the xenon arc photocoagulator which showed a decrease in proliferation in treated eyes. This study is interesting because it included a period of study to assess the change of the retinopathy before treatment was begun.

A recently published study[18 19] compared the effect of xenon arc and argon laser in the treatment of disc neovascularisation in 21 patients and found no difference in the effect on disc vessels and visual acuity, but there was greater functional loss after xenon treatment.

Patients and methods

Sixty-three patients attending the St Thomas's Hospital Diabetic Retinopathy Clinic who had optic disc neovascularisation were selected for participation in the trial. No exclusion was made on the grounds of type or degree of diabetic control, though patients were included only if the following criteria in the examined eye were met with: (1) no previous photocoagulation; (2) no retinal detachment and not more than a minor degree of retinitis proliferans; (3) absence of rubeosis or glaucoma; (4) media clear enough to allow adequate photocoagulation. In 17 patients both eyes were entered into the trial and each eye was randomly allocated to a treatment group.

At the beginning of the study eyes were randomly allocated to an argon laser or xenon arc treatment group. At a later stage we decided to investigate the effect of incomplete retinal photocoagulation, as it seemed likely that some patients might benefit from peripheral treatment only. Therefore patients were then allocated to an argon laser group or xenon arc group and further allocated to a total or peripheral treatment group. 'Peripheral' treatment was the area treated by the contact lens mirror (peripheral zone in diagram). 'Total' treatment was the usual panretinal photocoagulation (intermediate and peripheral zone, Fig. 1).

RETINAL TREATMENT AREAS

There were therefore 6 groups in all: the original argon laser and xenon arc groups and subsequently the 4 subgroups: argon total, argon peripheral, xenon total, and xenon peripheral. Argon laser treatment was administered via a 3-mirror contact lens after topical application of a local anaesthetic. Xenon arc treatment was administered after a retrobulbar injection of 2% lignocaine. Some patients receiving argon laser treatment required a retrobulbar injection of lignocaine if the treatment became painful. Argon laser treatment was delivered by a Coherent Radiation System 800 argon laser with 0·1–0·2 second duration and a 500 μm burn size. Xenon treatment was delivered by the O'Malley Log 2 xenon arc photocoagulator with up to 1·0 second burn duration and 4·5° cone size (the end point of treatment was taken as the first sign of retinal whitening). Xenon treatment was usually given in 2 sessions. Argon treatment was given in 2 to 4 sessions.

The results of treatment are based on recordings before beginning therapy, and the follow-up period is dated from the completion of treatment (in the 'total' treatment area groups no further therapy was given in the follow-up period). The results of treatment were recorded on a proforma, which included details of corrected visual acuity and a grading of the retina and disc new vessels according to the Hammersmith method.[20]

The response to treatment was determined by observing the visual acuity and grading of new vessels on the disc over a period of 2 years after treatment. To compare the treatment it was then necessary to assess how the trends in visual acuity (on a scale of 1 to 9: 6/5 to <6/60) and disc grading (on a scale of 1 to 5) differed over time. In the analysis each subject was allowed to have his own pattern of response over time and then the average difference between the treatment groups was assessed. This was done after taking into account factors which might influence response,

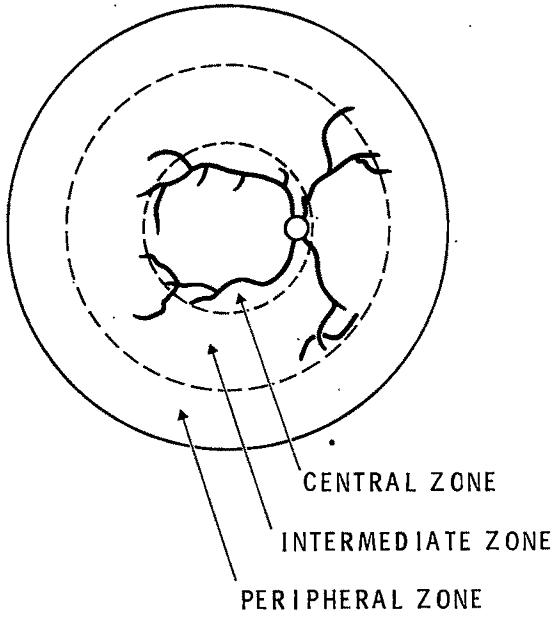


Fig. 1 *Photocoagulation treatment areas.*

Table 1 *Average duration of diabetes before treatment according to age of onset of diabetes*

Age of onset (years)	*No.*	*Mean duration of diabetes before treatment (years)*	*Range (years)*
1–20	21	22	7–38
21–40	18	18	1–35
41–60+	22	6	1–22

Table 2 *Length of follow-up in all treatment subgroups*

	Range (months)	*Average follow-up (months)*
Xenon	2–40	22
Xenon periphery	1–22	9
Xenon total	1–40	17
Argon	1–47	20
Argon periphery	2–32	12
Argon total	1–36	14

Table 3 *Number of eyes in each treatment group at the beginning and end of study (after 2 years of follow-up)*

	Baseline		*End of study*	
	VA	*NVD*	*VA*	*NVD*
Xenon	19	19	7	10
Xenon peripheral	9	9	2	3
Xenon total	12	12	6	6
Argon	16	16	8	7
Argon peripheral	13	13	3	3
Argon total	11	11	4	4
Total	80	80	30	33

VA=visual acuity. NVD=new vessels on disc.

Table 4 *'Peripheral' treatment patients given additional treatment*

Peripheral treatment group	*No. of eyes*
Xenon	4
Argon	5

Table 5 *Visual acuity (− =deterioration; + =improvement)*

Treatment	*Initial No. of eyes*	*Time interval (months)*			
		0–3	*3–6*	*6–12*	*12–24*
Xenon	19	−1·1	−0·2	−0·4	−0·8
Xenon peripheral	9	+0·3	−0·5	−0·6	+0·3
Xenon total	12	−0·4	−0·9	−0·7	−1·2
Argon	16	+0·1	−0·1	−0·4	−0·2
Argon peripheral	13	−0·2	0·0	+0·4	+0·2
Argon total	11	−0·8	+0·5	−0·8	−0·3

Table 6 *Optic disc neovascularisation based on a grading system 1–5[20](− = deterioration, + = improvement)*

Treatment	*Initial No. of eyes*	*Time interval (months)*			
		0–3	*3–6*	*6–12*	*12–24*
Xenon	19	+1·2	+1·0	+1·5	+1·5
Xenon peripheral	9	+1·1	+1·2	+1·4	+1·6
Xenon total	12	+0·9	+1·0	+1·6	+1·6
Argon	16	+0·9	+0·8	+0·6	+1·0
Argon peripheral	13	+1·0	+0·4	+1·5	+2·0
Argon total	11	+0·8	+1·7	+1·7	+1·1

for example, age, sex, and duration of diabetes. The analysis was performed with the statistical program GLIM[21] with the facilities of the London University Computer Centre.

The 63 patients involved in the study ranged in age from 21 to 74 years (mean 47·5 years), and the duration of diabetes (from diagnosis to date of first treatment) varied from less than a year to 38 years (mean 14·2 years). The average duration of diabetes before treatment in the juvenile diabetic group (under 41 years) was 20 years and in the group aged over 40 was 6 years (see Table 1). There were 37 male (58·7%) and 26 female patients (41·3%).

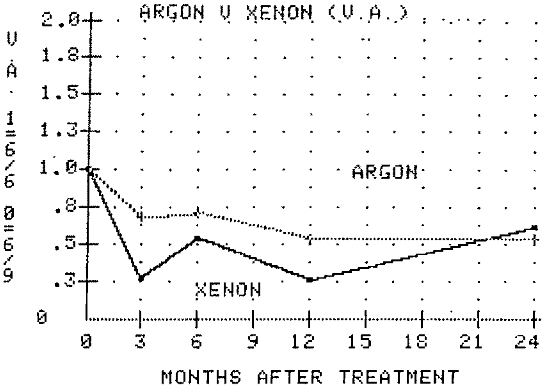
The maximum follow-up time in the xenon arc groups was 40 months and in the argon laser groups was 47 months (see Table 2 for range and average follow up time in each treatment group). The number of eyes assessed in each subgroup at the beginning and end of the study is given in Table 3.

Results

INADEQUATE TREATMENT RESPONSE

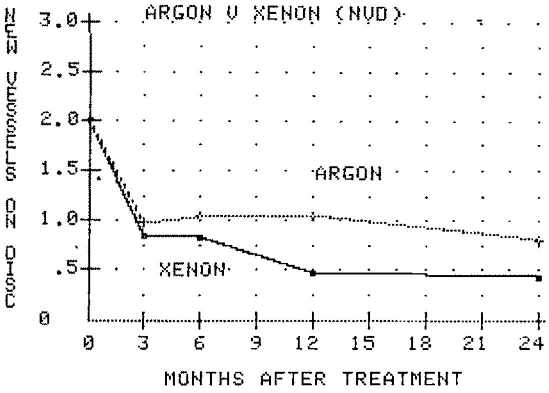
It was decided when following up patients that if a complete regression of disc neovascularisation was not achieved from peripheral treatment then further treatment of the same type would be given in the intermediate zone, and observation was continued to determine the effect of this delay in completing panretinal photocoagulation (Table 4). Patients who received further treatment of a different type were withdrawn from the study.

Table 5 shows the average change in visual acuity (lines on the Snellen chart) when compared with the pretreatment value in the 6 subgroups at various time intervals. There is no clear pattern, but since the number of individuals observed at each time interval was variable the picture may be misleading. This also applies to the results shown in Table 6 (disc neovascularisation based on Hammersmith grading code). Therefore regression analysis was performed allowing for this problem while estimating the average trend in each group by the GLIM statistical program.



PLOT 1 (5 PTS)			PLOT 2 (5 PTS)		
POINT#	X(I)	Y(I)	POINT#	X(I)	Y(I)
1	0	1	1	0	1
2	3	0·27	2	3	0·68
3	6	0·53	3	6	0·71
4	12	0·26	4	12	0·54
5	24	0·61	5	24	0·53

Fig. 2 *A comparison of argon laser and xenon arc photocoagulation; average change of visual acuity over 2 years.*



PLOT 1 (5 PTS)			PLOT 2 (5 PTS)		
POINT#	X(I)	Y(I)	POINT#	X(I)	Y(I)
1	0	2	1	0	2
2	3	0·84	2	3	0·99
3	6	0·83	3	6	1·04
4	12	0·46	4	12	1·04
5	24	0·43	5	24	0·8

Fig. 3 *Comparison of argon laser and xenon arc photocoagulation; average change of disc neovascularisation over 2 years.*

The regression analysis used assumes that the response variables for visual acuity and optic disc neovascularisation were normally distributed. Obviously with integer codes this cannot be the case. Nonetheless the variation about the trends fitted in the analysis was found to be sufficiently close to normal for present purposes.

REGRESSION ANALYSIS:
ARGON LASER VERSUS XENON ARC

All results are based on the comparison of the treatment groups followed up for 2 years. The period of follow-up dates from the last day of the treatment course; no further treatment was given during this period.

VISUAL ACUITY

On comparison of argon laser and xenon arc panretinal photocoagulation no significant difference in the effect on visual acuity was noted. Fig. 2 shows the average trend in visual acuity over 2 years for each treatment type, estimated from the regression model that would be expected from a hypothetical '6/6' eye (NB: it is the nonparellelism between the 2 treatments and the difference thus shown which are important rather than the absolute visual acuities). All 4 graphs in this section are plotted by a similar method.

NEW VESSELS ON THE DISC

Xenon arc treatment produced an average improvement of 1·5 grades at 24 months; the response to argon was an improvement of one grade at 24 months. However, this difference did not reach statistical significance. Fig. 3 gives the estimated average response to treatment over time for a hypothetical eye with an initial new vessel grading of 2.

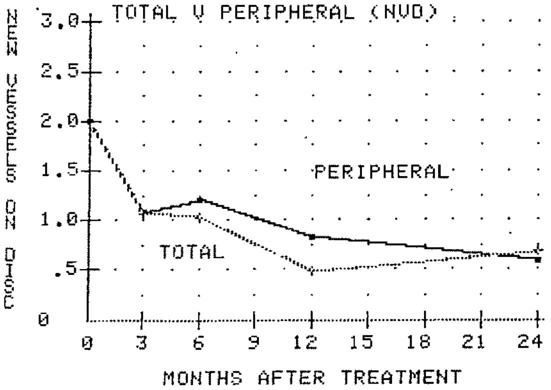
This shows that most of the response occurs in the first 3 months and is almost identical for both treatments, so there is little to choose between them in the speed of response. There is only a slight improvement over the subsequent 21 months.

This is a regression model based on a hypothetical eye and therefore the fact that the graph does not reach zero at 24 months does not necessarily mean that complete regression of disc vessels was not achieved in the majority of cases. In fact only 6 patients failed to respond completely (see Table 7). This failure to respond was defined as the presence of

Table 7 *Analysis of patients with an inadequate response*

Treatment	*Sex*	*Age*	*Duration of diabetes*	*Initial NVD*	*Final NVD*	*Time interval (months)*
Argon	F	34	6 months	3	1	40
Argon	M	52	7 months	2	1	34
Argon	F	47	13 years	2	2	12
Xenon	F	52	14 years	2	1	*31
Xenon	M	56	18 months	3	1	40
Xenon	F	46	2 years	5	1	34

*This patient received argon treatment at this stage.
NVD=new vessels on disc.



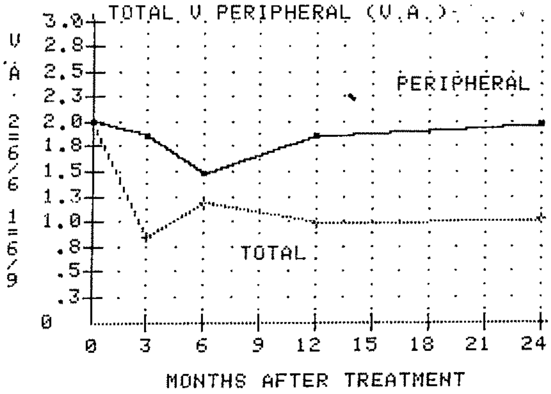
PLOT 1 (5 PTS)

POINT#	X(I)	Y(I)
1	0	2
2	3	1·08
3	6	1·21
4	12	0·82
5	24	0·59

PLOT 2 (5 PTS)

POINT#	X(I)	Y(I)
1	0	2
2	3	1·06
3	6	1·03
4	12	0·49
5	24	0·69

Fig. 4 *Comparison of total and peripheral treatment areas; average change in disc neovascularisation over 2 years.*



PLOT 1 (5 PTS)

POINT#	X(I)	Y(I)
1	0	2
2	3	1·85
3	6	1·49
4	12	1·86
5	24	1·97

PLOT 2 (5 PTS)

POINT#	X(I)	Y(I)
1	0	2
2	3	0·85
3	6	1·18
4	12	0·98
5	24	1·03

Fig. 5 *Comparison of total and peripheral areas of treatment; average change in visual acuity over 2 years.*

disc vessels at least 12 months after the initial treatment course.

The main similarities between these patients are that their age of onset of diabetes falls in the range 30-50+ years, and they all had fairly marked disc neovascularisation when treatment was started.

COMPARISON OF PERIPHERAL AND TOTAL GROUPS

Since no significant difference between the argon and xenon treatments was noted, the different treatments were combined to determine the difference, if any, between the effect of treating the retinal periphery only and a standard panphotocoagulation. The pattern of response estimated from the regression model is shown in Figs. 4 and 5. In neither case was the difference significant, though there was a slight suggestion that peripheral treatment produced better visual acuity results. This result occurs partly because there was a farily high incidence of withdrawal of patients (13 out of 22) who were unsatisfactorily responding to peripheral treatment. Therefore towards the end of the 2-year period the peripheral group consisted of a selected group of good responders.

An analysis of the cases withdrawn from this part of the study was performed. Of a total of 22 peripherally treated patients 13 were given extra treatment or withdrawn. These were compared with those remaining in the study. There was no significant difference in visual acuity, disc neovascularisation grading, retinal grading, and mean age between the groups. Of these patients 9 received further treatment of the same type; 4 xenon group patients improved on average by one disc grading during the period after extra treatment. Five patients in the argon laser group showed on average no changes in disc grading after further treatment.

Discussion

The main conclusion from this trial is that, when they are used with the technique described above, there is little to choose between argon laser and xenon arc in their effectiveness. Xenon arc treatment appears to be slightly more effective, but the difference is not statistically significant Fig. 3.

The results obtained when comparing the peripheral and total treatment groups suggest that there may be a case, in suitable patients, for initially treating the peripheral area only, and only at a later stage 'filling in' the central area if neovascularisation occurs. However, on comparison of the group of patients who responded well to peripheral treatment with those who did not respond there was no way of predicting the outcome of treatment from the initial fundus examination or other patient characteristics. Furthermore after further treatment to the intermediate zone, i.e., to complete the panphotocoagulation, the response has not been completely satisfactory. Whether this means that delaying the full panphotocoagulation is detrimental to the outcome or whether these are patients who do not respond particularly well to treatment is not clear. It does suggest that at present the safest course is probably to pursue a technique of complete panphotocoagulation from the outset.

CONCLUSIONS

We have shown that there is no significant difference between the 2 treatments in the effect on visual acuity and disc neovascularisation and that treatment of the peripheral retina only is inadequate in many cases of proliferative retinopathy. Previous studies have shown a higher incidence of visual field loss and difficulty with night vision with xenon arc.[10–13] Therefore it appears that these factors should be the main deciding points when contemplating the choice of photocoagulator in the treatment of proliferative diabetic retinopathy.

We are grateful to Mrs Margaret Grice for her secretarial assistance. Dr A. P. Plumb is an Iris Fund research fellow.

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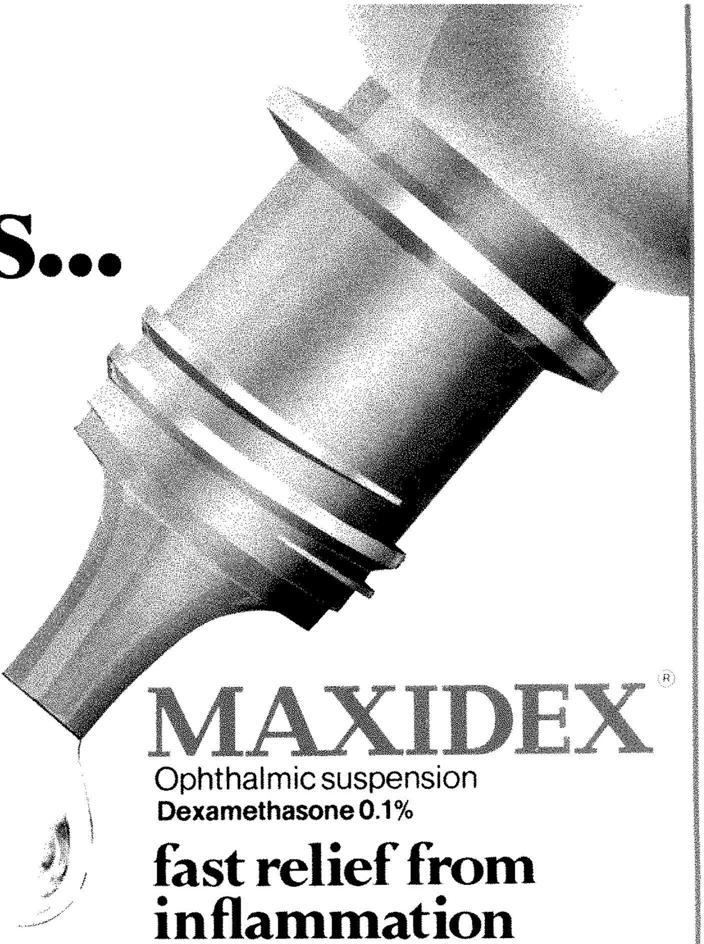

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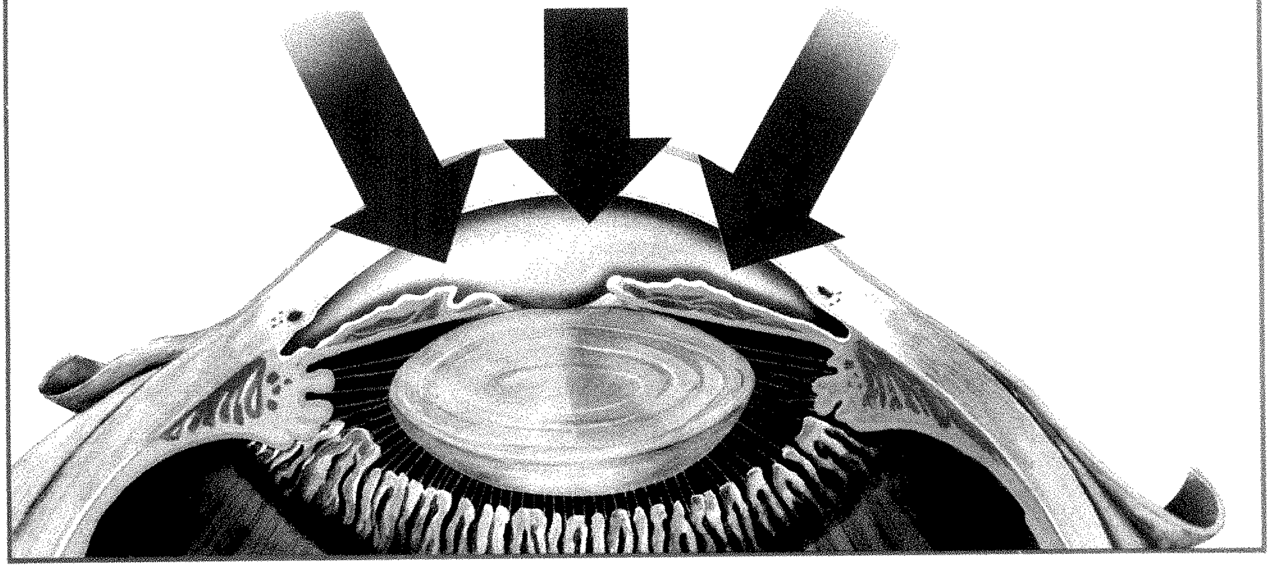

Prescribing information

Presentation Dexamethasone 0.1% in a vehicle containing 0.5% hydroxypropyl methylcellulose (hypromellose). A sterile isotonic ophthalmic suspension. **Clinical Uses** Maxidex is indicated in the treatment of certain inflammatory conditions of the anterior segment. Acute and chronic anterior uveitis, iritis, iridocyclitis, cyclitis, herpes zoster ophthalmicus. External diseases: non-specific superficial keratitis. Phlyctenular kerato-conjunctivitis, vernal conjunctivitis, allergic, catarrhal and non-purulent conjunctivitis. Recurrent marginal ulceration of toxic or allergic aetiology. Thermal or chemical burns. Post-operatively to reduce inflammatory reactions. **Dosage and Administration** For severe or acute inflammations 1 or 2 drops to be instilled into the eye every 30-60 mins. for at least 3-4 days or until a satisfactory response is made. Then every 2 to 3 hours for one to two weeks. If a favourable response is not obtained in 3-4 days subconjunctival or systemic therapy should be instituted. **Contra-Indications** Herpes simplex and other viral diseases of the cornea and conjunctiva. Fungal disease. Tuberculosis and acute purulent untreated infections. **Warnings** Extended use of topical steroids may increase intraocular pressure which should be checked frequently. In those diseases causing thinning of the cornea, perforation has been known to occur with the use of topical steroids. If the inflammation does not respond within a reasonable period other forms of therapy should be instituted. If any reaction indicating sensitivity is observed, discontinue use. In cases of bacterial infections concomitant use of antibiotics or chemotherapeutics is mandatory. Intensive or prolonged topical corticosteroid therapy is a possible factor in the formation of posterior subcapsular cataracts. **Pregnancy Warning** Although topical steroids have not been reported to have an adverse effect on pregnancy the safety of their use in pregnancy has not been absolutely established, therefore it is advisable not to use this product for long term treatment of pregnant patients. **Pharmaceutical Precautions** Maxidex should be stored in a cool place away from direct sunlight. Keep the container tightly closed. The contents should be discarded one month after opening. Shake well before using. **Legal Category** P.1. T.S.A. POM **Package Quantity** 5 ml and 15 ml containers. **Further Information** Maxidex eye drops are contained in an unbreakable, semi-rigid, plastic dropper bottle with a screw-on cap, containing 5 ml or 15 ml of the preparation. This container bears the label and is itself in a rigid capped plastic outer. Maxidex is a highly penetrating form of dexamethasone (0.1%) microfine suspension especially formulated to provide maximum corneal absorption. **Product Licence** 0649/5914 **Product Licence Holder** Alcon Laboratories (UK) Limited, Imperial Way, Watford, Hertfordshire. Additional information available on request.

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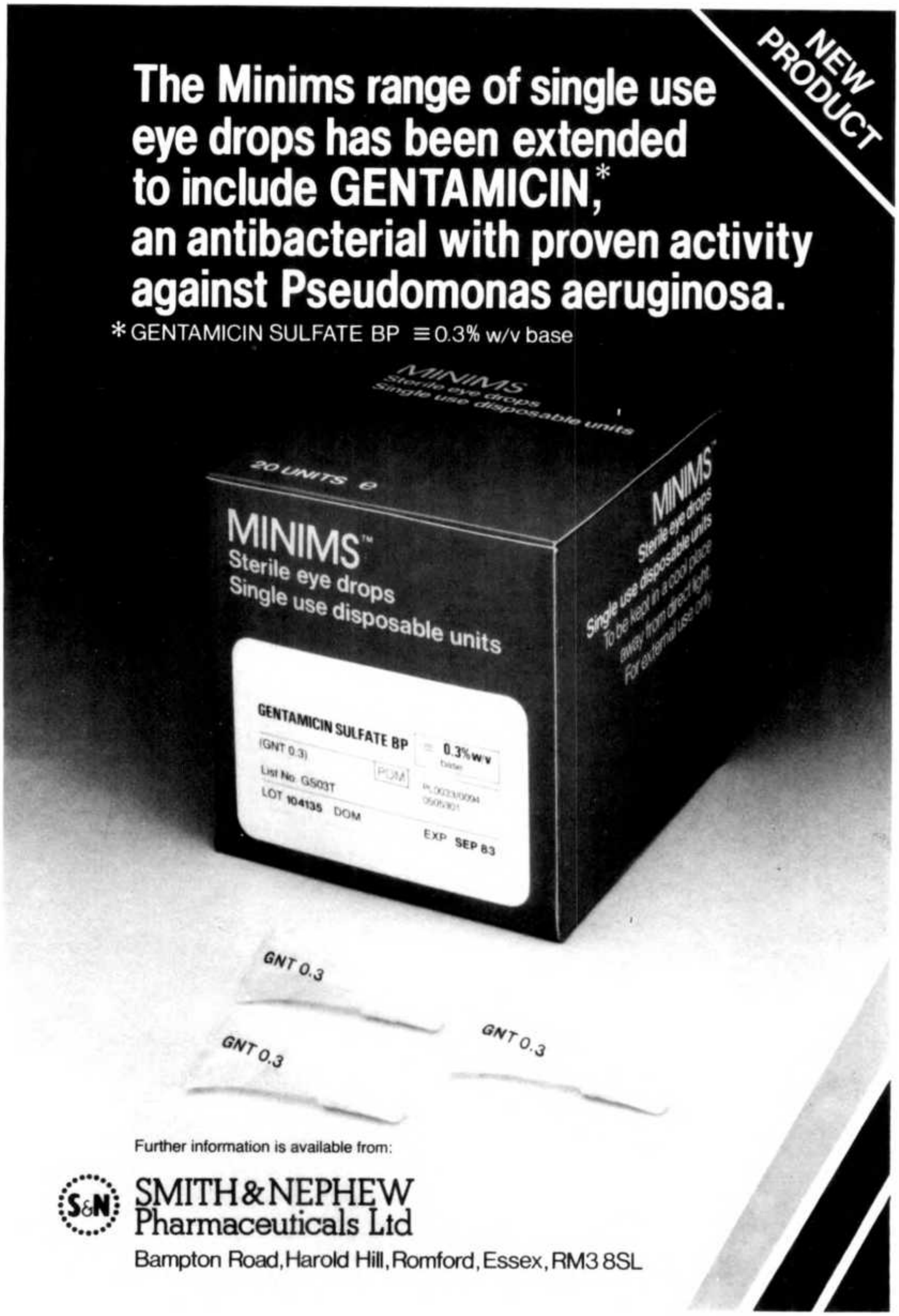

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British Journal of Ophthalmology, 1982, **66**, 219–226

A clinicopathological case report of retinopathy of pancreatitis

MARILYN C. KINCAID, W. RICHARD GREEN, DAVID L. KNOX, AND CHARLES MOHLER

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SUMMARY A 32-year-old black woman with pancreatitis developed visual loss in both eyes. On ophthalmoscopic examination she had extensive ischaemic infarcts at the posterior poles of both eyes, a clinical picture which has been reported previously in patients with pancreatitis and noted to be similar to Purtscher's retinopathy. On histopathological examination of the eyes after death there were arteriolar occlusions in both the choroid and retina and inner ischaemic infarctions with inner retinal oedema. Owing to the 23-day interval from arteriolar occlusion until death the exact nature of the original occlusion could not be determined. However, either fat emboli or activated complement C5-induced granulocyte embolus formation are possible causes.

Purtscher[1] first described in 1910 the retinopathy that now bears his name. It occurs after trauma to the head[1] or the body[2] and is characterised by visual loss within hours and the appearance of cotton-wool spots and haemorrhages at the posterior pole. More recently a similar fundus picture has been recognised in pancreatitis.[3 4] The pathogenesis remains obscure. Some have theorised that fat emboli play a causative role in some cases of Purtscher's retinopathy[5] and in the retinopathy of pancreatitis,[3] but others[6] dispute this view. Kelley[7] believed, on the basis of capillary leakage seen on fluorescein angiography performed within hours of injury, that primary endothelial damage was a more likely cause. However, he could not rule out microemboli.

More recently the role of granulocyte emboli formed by complement activation, specifically C5-induced granulocytic clumping, has been proposed as the aetiology in both Purtscher's retinopathy and in the retinopathy of pancreatitis.[4]

Case report

The patient was a 32-year-old chronic alcoholic woman. She was admitted to the medical service on 21 May 1972 with epigastric pain and a 3-day history of anorexia. At the time of admission the liver was tender and palpable 3 cm below the right costal margin. There were skin ecchymoses, and a nasogastric tube drained guaiac-positive coffee-ground material. Her blood pressure was 160/90 mmHg. Platelet count, white cell count, and clotting times were normal. Haematocrit was 30%. Amylase was 208 CRW units (normal=20–160). Haemoglobin electrophoresis was normal.

On the evening of 22 May she had a tonic-clonic seizure and became comatose for 3 days. A neurological examination was normal except for the altered mental status. Arteriogram and echoencephalogram were normal, but the cerebrospinal fluid contained an elevated protein level of 118 mg/dl (1·18 g/l) (normal=15–45 (0·15–0·45 g/l)), with a normal glucose level. The neurologist noted 'occasional' dot haemorrhages, with retinal oedema in both eyes. The amylase rose to 372 CRW units, and she developed a fever, for which she was given kanamycin and chloramphenicol.

On 24 May 1972 she was seen by one of us (D.L.K.) and found to have diffuse intra- and subretinal oedema, with narrowed retinal arterioles in both eyes. There were a few retinal haemorrhages. This was thought to be consistent with hypertensive retinopathy. Because of her obtunded state her vision could not be tested.

Her amylase continued to rise, up to 720 units. Calcium was low at 5 mg/dl (1·25 mmol/l) (normal=

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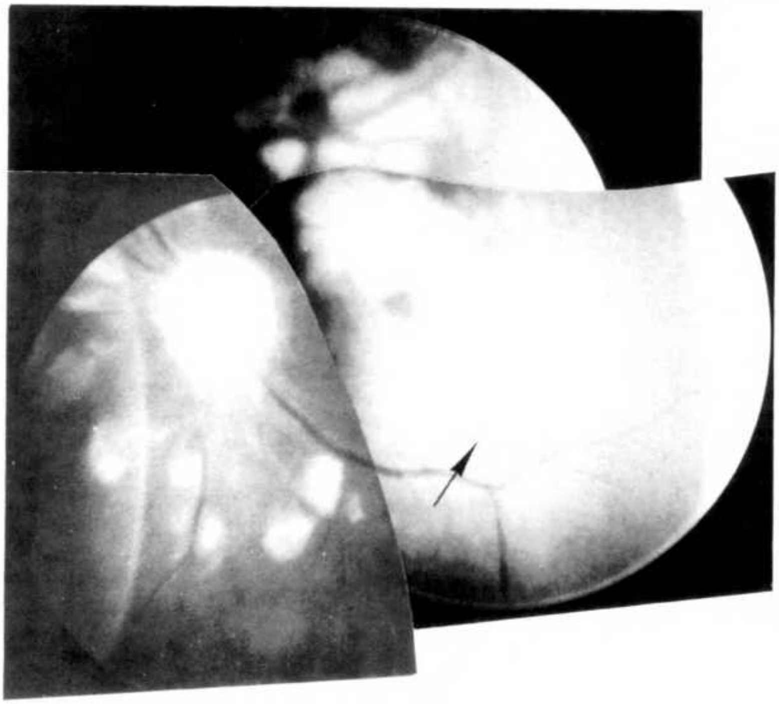

Fig. 1 *Composite photograph of left eye taken at the bedside. The macula appears as a cherry-red spot, and fluffy-white exudates are seen throughout the posterior pole. The arterioles (arrow) are narrowed.*

9–11 (2·25–2·75 mmol/l)), and albumin was low at 1·7 g/dl (17 g/l) (normal=3·5–5·5 (35–55 g/l)). However, as the amylase level fell, her mental status improved.

Because of a low haematocrit she was transfused, but developed pulmonary oedema, responsive only to repeated phlebotomies. On 26 May 1972 *Pseudomonas aeruginosa* was grown from her lungs. She continued to have intermittent gastric bleeding, with a drop in the haematocrit. Gastroscopy disclosed massive gastritis.

On 1 June 1972 funduscopic examination by one of us (D.L.K.) revealed pallor and oedema, narrowed arterioles, and subretinal dense white exudate, thought possibly to be lipid. The pupils were reactive but sluggish.

The following day another ophthalmologist saw the patient. He described the deposition of a 'white opalescent coagulum' within the sensory retina in the posterior pole. Arteriolar narrowing was still apparent, and because of the retinal oedema the macula appeared as a cherry-red spot (Fig. 1). He believed that this was a form of lipaemia retinalis consistent with hyperlipidaemia secondary to her pancreatitis, along with hypertensive small-vessel disease. However, although the cholesterol level was 467 mg/dl (12 mmol/l) on the day of admission, two days later it had dropped to 187 mg/dl (4·8 mmol/l), within the normal range, and it remained normal. The triglyceride level was 140 mg/dl (1·6 mmol/l), also normal.

As the pancreatitis resolved and the amylase and calcium levels fell towards normal her major problem continued to be bleeding from the gastrointestinal tract. Both prothrombin time and partial thromboplastin time remained prolonged, and she required repeated transfusions. Gastroscopy showed a possible specific lesion on the lesser curvature; so on 11 June she underwent a total gastrectomy, vagotomy, and oesophagojejunostomy. Postoperatively she became oliguric, with rising blood urea nitrogen and creatinine. Since the haematocrit had again fallen, she was re-explored surgically the following day, but no bleeding lesion was found. She was given kanamycin and penicillin for possible sepsis, and was dialysed peritoneally. On 14 June she developed pulmonary oedema, which improved with phlebotomy. However, she became unresponsive with multiple organ failures and died on 15 June 1972.

Necropsy disclosed pancreatitis with fat necrosis of the body and tail of the pancreas, massive gastrointestinal haemorrhage, and necrotising haemorrhagic bronchopneumonia consistent with the clinically observed pseudomonas infection. The kidneys showed hyaline scarring and interstitial fibrosis consistent with hypertension. The brain

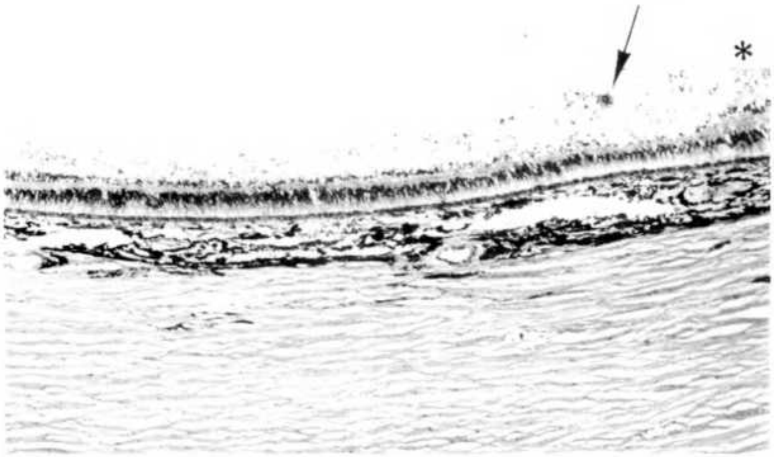

Fig. 2A *Low-power view of the left eye showing diffuse oedema extending throughout inner retina. There is partial loss of the nerve fibre, ganglion cell, and inner plexiform layers and inner portion of the inner nuclear layer. The area of transition from normal retina is fairly abrupt (asterisk). An occluded vessel (arrow) is present. (Haematoxylin and eosin, ×57).*

contained small haemorrhages in the cortex and also the right hippocampus, with bacteria in the necrotic vessel walls. The brain lesions were thought to be similar to those of the lung and could have arisen in a single embolic episode. However, they were believed to be too recent to explain the original neurological symptoms. There was no definite evidence of pseudomonas lesions elsewhere.

Material and methods

Both eyes were obtained at necropsy and were routinely fixed in a buffered solution of 4% formaldehyde for several days. They were then washed in water and dissected in 60% alcohol. The external gross appearance was unremarkable and the eyes were of normal size. They were opened

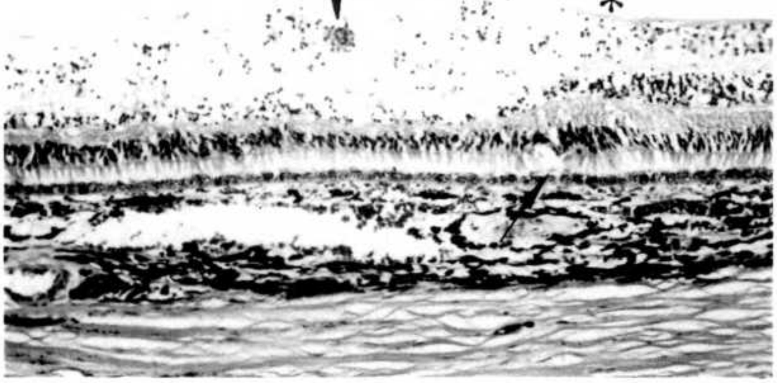

Fig. 2B *Higher power view of the same area showing the abrupt transition (asterisk) from normal to oedematous retina. An occluded arteriole (arrow head) is present. A focal area of photoreceptor disruption (arrow) overlying apparently normal RPE is present. (Haematoxylin and eosin, ×109).*

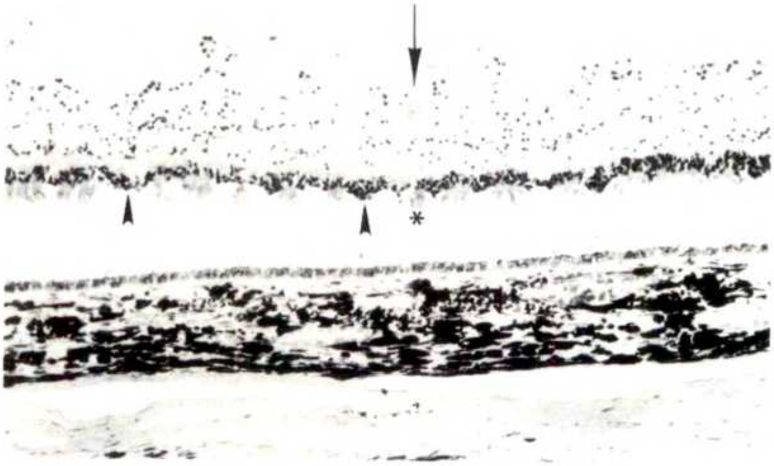

Fig. 3A *Full thickness of retina of the right eye with inner retinal oedema and also disruption and loss of photoreceptors. There is outer segment (asterisk) and inner segment (arrowheads) loss. The underlying RPE and choroid appear normal. An occluded retinal arteriole (arrow) is present. (Haematoxylin and eosin, ×120).*

horizontally, and whitish material, thought to be exudate, was present in the posterior poles of both eyes. The pupil-optic nerve portions were then routinely dehydrated and embedded in paraffin, and 0·1 mm stepped sections taken for light microscopy.

In each eye, within the caps, areas of retinal vascular occlusion could be identified grossly. Therefore, portions of retina which included the vascular occlusions were dissected from the caps and refixed in a buffered 2·5% glutaraldehyde-formaldehyde solution, rinsed in phosphate buffer, postfixed in 2% osmium tetroxide, dehydrated with graded acetone solutions, and embedded in Epon/Araldite for transmission electron microscopy. The remainder of the retina from the caps was trypsin-digested to study the vasculature.

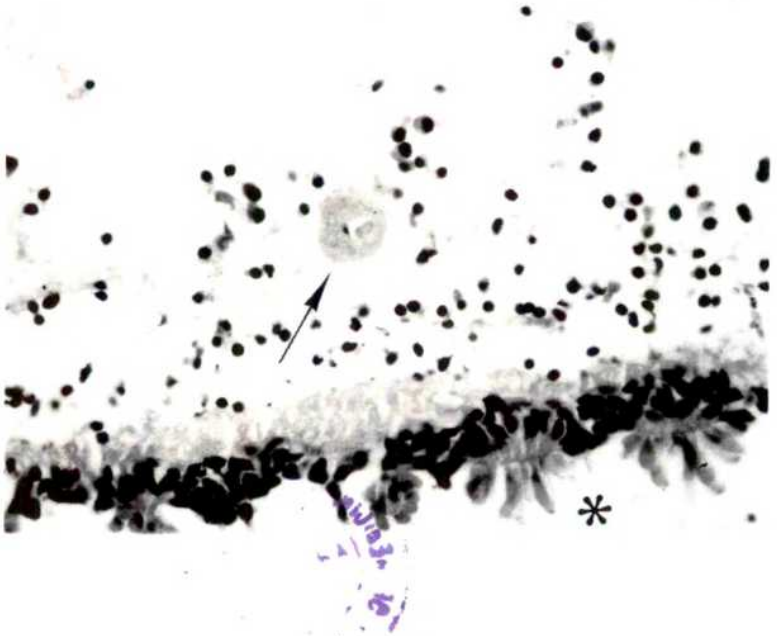

Fig. 3B *Occluded retinal arteriole (arrow) within an area of oedematous inner retina. There is also disruption and loss of photoreceptors (asterisk). (Haematoxylin and eosin, ×356).*

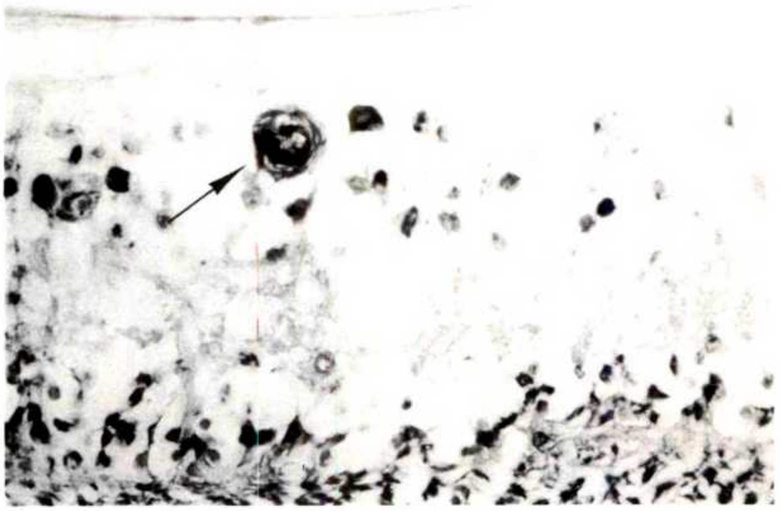

Fig. 3C *Another area of retina showing an arteriole completely occluded by fibrin. (Phosphotungstic acid-haematoxylin, ×471).*

Results

Both eyes showed similar changes. The anterior segments were normal except for some red blood cells in the anterior chamber of the right eye. The peripheral retina of both eyes showed typical peripheral cystoid degeneration. Posteriorly there were focal areas of oedema within the inner layers of the retina, with cystoid spaces and disruption of the normal architecture (Fig. 2). Transition from normal to oedematous retina was abrupt. In some areas there was also disruption of the photoreceptors, with loss of photoreceptor segments (Fig. 3). In these areas outer segments, and to a less extent, inner segments were missing, with the remaining photoreceptors displaying a curious bunching together at the outer nuclear layer. However, the underlying retinal pigment epithelium (RPE) and choroid remained normal. In both eyes occluded retinal arterioles were present (Fig. 3B). The occluding material was periodic-acid-Schiff positive. A special stain for fibrin was positive (Fig. 3C). Small haemorrhages were present in the outer plexiform layer (Fig. 4). No occlusions were seen in the material prepared by trypsin digestion. At other levels occluded choroidal vessels were evident which also contained fibrin (Fig. 5).

Electron micrographs revealed small arterioles with narrowed lumina containing proteinaceous material centrally, consistent with recanalised thrombi.

OF MEDICINE

Discussion

This patient presented with a fundus picture classic for Purtscher's retinopathy, with cotton-wool spots and inner retinal oedema centred round the optic nerve and extending to the macular area.[1,2] This fundus appearance has been described in acute pancreatitis also,[3,4] but no histopathologic correlation has been available in cases of pancreatitis.

The histopathological findings in our patient support the clinical picture. The inner retinal oedema was widespread, with abrupt transition from normal to oedematous retina. In much of the involved area there were striking changes in the photoreceptor cells. We suggest that the effect of inner retinal distension is to cause the outer retinal layers to become bunched and squeezed together. Such distension might therefore account in part for the changes seen in the photoreceptors. Impairment of choroidal circulation alone was probably not responsible, as the retinal pigment epithelial cells remained normal.

Unfortunately, because of the severity of her illness and altered mental state, the patient's vision was not tested nor could a fluorescein angiogram be done. It seems evident, however, that the retinopathy and possibly the neurological findings were caused by her pancreatitis and not, for instance, due to emboli from the pseudomonas infection of the lung, which occurred much later in the disease course.

It is possible to separate Purtscher's retinopathy

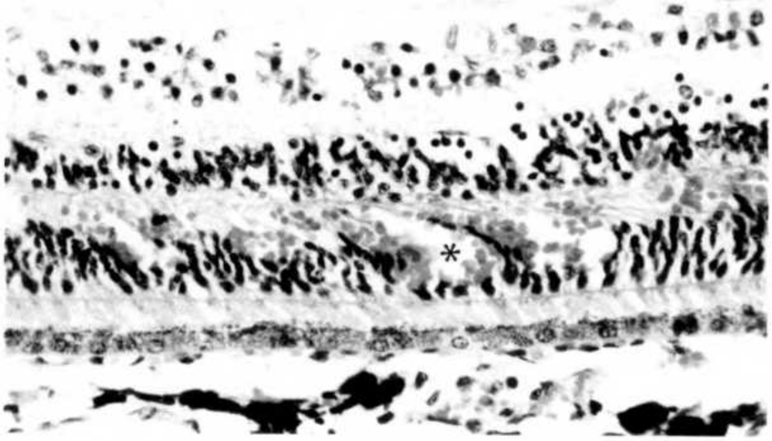

Fig. 4 *A haemorrhage (asterisk) in the outer plexiform layer of the retina of the left eye. (Haematoxylin and eosin, ×284).*

into 2 types in accordance with aetiology: retinopathy caused by fat emboli, and retinopathy caused by sudden elevation in the intravascular pressure.

The first histological evidence for fat emboli causing Purtscher's retinopathy was provided by Urbanek[5] in 1934. Seven of his patients had long-bone fractures and developed retinopathy. He obtained the eyes from 3 of them and demonstrated emboli in the retina and choroid which histologically were positive for fat.

Since then, there have been other case reports[8-10] in patients with multiple injuries. These 3 reports all describe patients with extensive injuries and multiple fractures. Examination of the eyes and other body tissues with special stains post mortem disclosed numerous fat emboli throughout. Fat embolism can

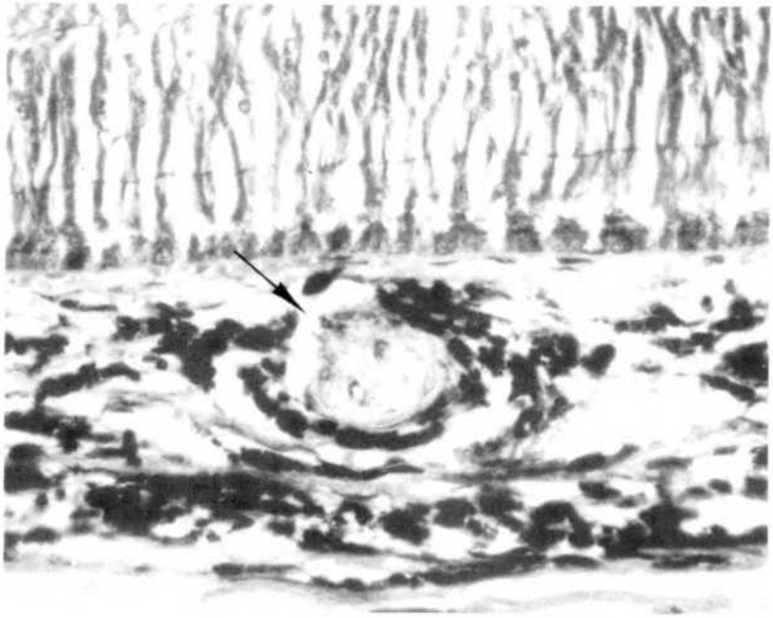

Fig. 5 *Occluded choroidal artery (arrow) in the right eye. The occluding material is fibrin. The overlying retinal pigment epithelium appears normal. (Phosphotungstic acid-haematoxylin, ×400).*

also occur after surgery to fatty areas, such as the breast.[11]

In Purtscher's[1] original report all the patients had sustained head trauma. He suggested that trauma to the head was transmitted by the cerebrospinal fluid around the optic nerves with resultant stasis and passage of perivascular lymph into the retina.

Marr and Marr[2] in their review noted that sudden elevation of intrathoracic pressure caused by direct trauma or deceleration forces could produce the picture of Purtscher's retinopathy. They postulated that this was due to increased venous back pressure causing haemorrhage, small vessel occlusion, and retinal oedema.

Several antecedent injuries producing sudden elevation in intravascular pressure have been described. Fundus changes were followed as they evolved in a pilot who ejected from his jet travelling at supersonic speed.[12] One hour after injury there was arteriospasm with minimal haemorrhage but with visual acuity of counting fingers. The following day there were definite haemorrhages, both flame shaped and round, along with cotton-wool patches. By the following day all findings were more pronounced, with subhyaloid haemorrhages. On the fourth day oedema was more generalised, giving the macula a cherry-red appearace. However, his vision did improve. Slowly the haemorrhages and oedema resolved, with the patient regaining normal visual acuity and fundus appearance after 3 months.

Gass[6] considered that Purtscher's retinopathy from chest compression is probably caused by capillary damage. Fluorescein angiography in the patient he described showed collapse and late leakage of the capillary bed in the area of the optic nerve, where the haemorrhages and exudates were. His patient later developed optic atrophy.

Kelley[7] was able to examine a patient within an hour of chest compression by a lap and shoulder seat belt in a car accident. Fundus abnormalities, including superficial exudates, perimacular oedema, and haemorrhages, were evident in the right eye within an hour of the accident. But fluorescein angiography done within 2 hours of injury showed leakage from small vessels in both eyes. Unlike the patient reported by Gass,[6] this patient had no areas of nonperfusion. Kelley[7] favoured the possibility of direct damage to the capillary endothelium as most likely, although he believed microemboli could not be ruled out as a cause. His patient's vision returned to normal within 2 weeks, but the fundus appearance did not resolve until 10 weeks after the injury.

Some patients with a typical Purtscher's retinopathy sustained minor trauma, such as a fall from a bicycle or gymnastic equipment, without the loss of consciousness.[2] The authors suggested that such injuries might result in a transient rise of the venous pressure within the head. The retinopathy in Purtscher's patients may be explained on the same basis.

Marr and Marr[2] pointed out that it can be difficult to separate the retinopathy of fat embolism from that of increased hydrostatic pressure, but thought that this can be done in part by the presence or absence of a fat-generating injury, such as a fracture, and associated systemic findings, such as pulmonary and cerebral involvement. In their opinion fat emboli produce retinopathy at least a day or two after the event, while in retinopathy from increased hydrostatic pressure the fundus findings appear within hours. They believed diffuse oedema, with a cherry-red appearance of the macula, is more probably due to fat emboli.

Duane[13] reported several patients with history of trauma and varying fundus pictures. He believed that the retinopathy classically called Purtscher's was caused by combined rapid rises of arterial and venous pressures. A combination of hard exudates, inner retinal haemorrhages, and arterial spasms were caused by arterial pressure rise, and retinal oedema, transudation, and preretinal haemorrhage were caused by venous pressure rise. He believed the fundus findings were too variable, with injuries sometimes too complex, to be ascribed simply to angiospasm or fat emboli.

Other hypotheses, by no means mutually exclusive, include air emboli[14] and granulocyte aggregates secondary to complement activation.[4]

Burton[14] thought air embolism to be an alternative possibility in chest compression injuries. He cited experimental work in which animals that died of chest compressive injuries had air emboli in the lungs; however, the eyes were not examined. Burton[14] also pointed out in his follow-up of 4 patients that fine pigmentary changes occurred in the posterior poles of 2 of them, suggesting that choroidal as well as retinal embolism had taken place.

It has been observed that acute pancreatitis can be associated with a similar retinopathy.[3] The authors presented 3 patients with pancreatitis who had blurred vision during the disease course. Two patients had fluorescein angiograms which showed areas of arteriolar and capillary nonperfusion and late leakage, consistent with numerous small emboli. The authors stated that fat emboli from omental adipose tissue, digested by enzymes released from the inflamed and damaged pancreas, were responsible for the eye findings, as fat emboli to other organs in pancreatitis had been demonstrated.[3]

In a more recent report of a fourth patient with pancreatitis and Purtscher's retinopathy[4] the authors speculated that, rather than emboli of fat, the emboli were aggregates of granulocytes caused by activated C5, a component of complement. The authors could not directly prove that the patient's retinopathy was due to aggregates of granulocytes or that in their patient complement C5 levels were elevated. However, they obtained acute and convalescent serum from 12 other patients admitted to hospital with pancreatitis, and showed that their serum would aggregate granulocytes in the acute stage of the disease but not after convalescence. They were able to demonstrate that either trypsin or activated C5 added to normal serum would also cause aggregation.

Experimental work in vitro has shown that complement factor C5, when activated, was the responsible factor in granulocyte aggregation, since anti-C5 antibody abolished all aggregation activity.[15] Furthermore the size of the aggregates would approximate that of the 15–40 μm glass spheres used by Ashton and Henkind[16] to produce a fundus appearance similar to Purtscher's retinopathy.

The authors[4] proposed that digestive enzymes are released from the pancreas when it is acutely inflamed and activate complement factor C5, which in turn aggregates granulocytes. This theory is also consistent with Purtscher's retinopathy from trauma, because acute trauma has been shown to activate several complement factors.[17] This would be another possible cause for the fundus appearance. It is quite likely that a combination of several factors, including hydrostatic pressure changes, fat emboli, air emboli, and granulocyte emboli, could be responsible.

Histopathologically we were able to demonstrate vascular occlusion at the posterior pole both in the choroid and in the retina of our patient. Because she died 23 days after admission, and 21 days from the time the retinopathy was first observed, it was not possible to characterise the emboli. Either lipid emboli or granulocytic aggregates are possible alternatives.

This study was supported in part by Research Grant 1 R01 EY-01684 from the National Eye Institute (Dr Green) and a grant from the Heed Foundation (Dr Kincaid).

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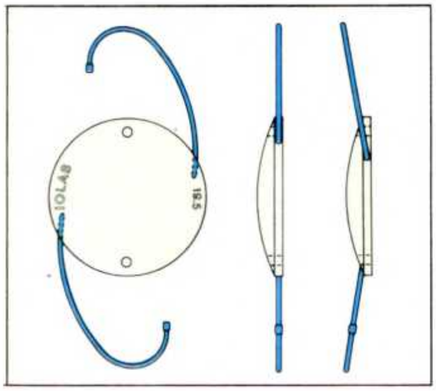

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British Journal of Ophthalmology, 1982, **66**, 227–229

Refractive errors in patients with fundus flavimaculatus

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SUMMARY A total of 59 patients (118 eyes) with fundus flavimaculatus who had atrophic macular lesions were examined for refractive error. Myopic refractions of greater than −0·1 dioptre were seen in 12% of a normal population and in 76% of our patient population. The spherical equivalent refractive errors described a single-peaked skewed distribution with a mean of −1·12 dioptres, which is 2·12 dioptres more myopic than that of a normal population. In addition astigmatic refractive errors of greater than +0·5 dioptres were found in 42% of this patient population, which is considerably more than the 18·6% observed in a normal population.

It has been previously recognised that an increased incidence of myopic and astigmatic refractive errors is present in certain heritable chorioretinal diseases. In a study of patients with congenital stationary night blindness with clinically normal fundi Carr found 13 of 14 patients to be myopic, with spherical equivalent refractive errors ranging from −2·00 to −14·00 dioptres (mean, −6·00 dioptres).[1] In a study of 134 retinitis pigmentosa patients Sieving and Fishman found a predominance of myopic refractive errors.[2] In their group the mean spherical refractive error was −1·86 dioptres, which is 2·96 dioptres more myopic than the normal mean of +1·00 dioptre.[3] Furthermore 74% of these retinitis pigmentosa patients had astigmatic errors greater than +0·5 dioptre[2] as compared with only 19% of a normal population.[3] Krill noted that 80 to 90% of patients with gyrate atrophy of the choroid and retina have myopia to variable degrees.[4] A similar increase in myopic and astigmatic refractive errors seemed to be present in patients with fundus flavimaculatus. To confirm this supposition we undertook a study of refractive errors in 59 patients with fundus flavimaculatus with associated atrophic macular lesions.

Patients and methods

Our study population consisted of 59 patients (118 eyes) with fundus flavimaculatus. All patients had an atrophic-like foveal lesion with either a ring or a more extensive garland of flecks within the posterior pole that extended to the equator in some instances. These cases have previously been described as stage I and stage II fundus flavimaculatus, respectively, by Fishman.[5] Patients with stage I and stage II fundus flavimaculatus without atrophic macular lesions were not included. Also excluded were patients with more extensive retinal pigment epithelial or choriocapillaris disease, described as stage III and stage IV fundus flavimaculatus, respectively, by Fishman.[5] In the latter group of patients there is more widespread atrophy of the retinal pigment epithelium and choriocapillaris, with extensive reabsorption of flecks, which makes the diagnosis of fundus flavimaculatus less apparent.

All refractive errors were obtained by manifest refraction. The majority were performed by one of the authors (D.D.); refractions from 3 patients were previously obtained by other physicians. The spherical refractive errors were calculated algebraically by adding one-half of the cylindrical correction to the spherical correction. Cylindrical refractive errors were measured and analysed in positive dioptres. None of the patients was aphakic.

Data on the refractive errors in the general

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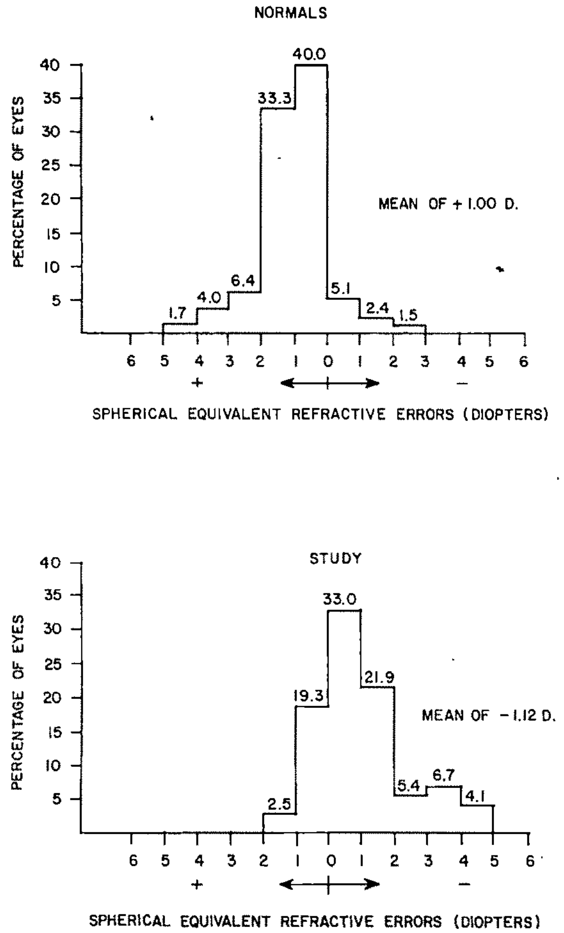

Fig. 1 *Spherical equivalent refractive errors from normal population compared with those of our fundus flavimaculatus patients.*

population were taken from a study by Sorsby *et al.*,[3] who sampled 1033 male National Service recruits in Great Britain in 1957 (aged 17 to 27 years). These authors included in their study a weighted addition of cases selected at random from a pool of men rejected from service because of high refractive errors. This study approaches an unbiased series of the general male population. A similar well controlled and unbiased series of the female population is unavailable.

Results

The spherical equivalent refractive errors for the 118 eyes studied ranged from +4·50 dioptres to −7·25 dioptres. The mean refractive error is 2·12 dioptres more myopic than the mean spherical equivalent refractive error of a normal population (Fig. 1). Myopic refractions of greater than −0·1 dioptre were seen in 12% of a normal population[3] and in 76% of our population. In addition there is a skew to the higher myopic refractive errors within the patient population. When the study group was subdivided into right, left, and best eyes (Table 1), a similar distribution was obtained. There was no statistical difference in the distribution of refractive errors between males and females. Furthermore there was no positive correlation between age and refractive error.

Table 1 *Percentage distribution of spherical equivalent in study population (n=59)*

Spherical equivalent (D)	*OD, %*	*OS, %*	*Best eye, %*
−8·0 to −7·1	1·7	1·7	1·7
−7·0 to −6·1	0	0	0
−6·0 to −5·1	0	0	0
−5·0 to −4·1	3·4	5·1	5·1
−4·0 to −3·1	6·8	6·8	8·5
−3·0 to −2·1	11·9	3·4	8·5
−2·0 to −1·1	25·4	22·0	25·4
−1·0 to −0·1	27·1	32·2	28·8
0 to +0·9	18·6	22·0	18·6
+1·0 to +1·9	3·4	5·1	1·7
+2·0 to +2·9	0	0	0
+3·0 to +3·9	1·7	0	1·7
+4·0 to +4·9	0	1·7	0

This study population also showed an increased incidence of cylindrical refractive errors. Cylindrical errors greater than +0·5 dioptre were found in 42% of the study population as compared with 19% of a normal population.

Discussion

Our analysis of refractive errors in patients with stage I and stage II fundus flavimaculatus with associated atrophic macular lesions showed a significant myopic shift of the mean spherical equivalent refractive error and a greater prevalence of astigmatic refractive errors, as compared with a normal population compiled by Sorsby *et al.*[3]

We note that Sorsby and coworkers derived their 'normal distribution' differently from that used for our fundus flavimaculatus population. For the 81% of their population who had cylinders less than or equal to +0·5 dioptre they used the same 'spherical equivalent' method as in our population. For the remaining 19% of their population, who had cylinders greater than +0·5 dioptre, they used the least ametropic meridian, a technique that understates the true spherical refractive error of the eye. Sorsby *et al.* found that astigmatic values greater than +0·5 dioptre were concentrated round the central spherical values and were proportionally more frequent with hypermetropic than myopic refractions. Thus, if their spherical errors were converted entirely to spherical equivalent values, the mean of their data would be slightly more hypermetropic than is presented here.

The significance as well as the explanation of our findings remain uncertain. Rabin and coworkers[6] have suggested from retrospective studies that an alteration in visual experience that disrupts pattern vision early in life, such as that which occurs in macular dystrophies, may result in a form of deprivation-induced myopia. Whether abnormalities in the cornea, lens, depth of the anterior chamber, or axial length of the globe singularly or combined are aetiological factors is yet to be determined. Such features are now being investigated in this population.

Morton F. Goldberg, MD, and Maxine Gere reviewed the manuscript; Juanita Waddy typed the manuscript.

This investigation was supported in part by core grant 1P30EYO1792 and grant EY-703802 from the National Eye Institute, National Institutes of Health, Bethesda, Maryland; by an unrestricted grant and Manpower award from Research to Prevent Blindness, Inc., NYC, and by a research grant from the National Retinitis Pigmentosa Foundation, Baltimore, Maryland.

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British Journal of Ophthalmology, 1982, **66**, 230–233

Primary choroidal and cutaneous melanomas, bilateral choroidal melanomas, and familial occurrence of melanomas

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SUMMARY The medical history of a patient with a familial atypical multiple mole melanoma syndrome revealed a combination of rare findings: occurrence of a melanoma in both eyes, development of 3 separate skin melanomas, and occurrence of other malignancies in the family. Another patient developed a choroidal and a skin melanoma, but there were no known malignancies in the family. A third patient with a choroidal melanoma had a mother with an ethmoidal melanoma.

The occurrence of primary malignant melanomas of the choroid and skin in the same patient is a rare phenomenon. In this paper the occurrence of both a primary choroidal melanoma and a primary cutaneous melanoma in 2 patients is reported. One of these patients had choroidal melanomas bilaterally and multiple cutaneous melanomas. The family study of this patient, described extensively elsewhere, provides evidence for the presence of the familial atypical multiple mole melanoma (FAMMM) syndrome[1 2] also referred to as B-K mole syndrome.[3] In a third patient with a choroidal melanoma the mother had had a melanoma originating from the ethmoidal sinus.

Case reports

CASE 1

A 57-year-old man was referred to our clinic in May 1978 for evaluation of an intraocular mass in his right eye. His medical history was significant in that a tumour with a small satellite lesion had been removed from the scalp at the age of 53; both proved to be malignant melanomas. At the age of 54 one melanoma was excised from the skin of his right shoulder and another from the gluteal region.

On admission visual acuity was 1/60 for the right eye and 6/6 for the left eye. Ophthalmoscopy revealed an elevated, darkly pigmented, solid choroidal mass arising from the temporal equatorial region in the right eye. It measured approximately 13 mm in diameter and 8 mm in elevation. At that time the ocular media of the left eye were clear, and on ophthalmoscopy no abnormalities were observed in this eye. Fluorescein angiography showed an early mottled fluorescence and late diffuse staining of the tumour. A 48-hour ^{32}P-uptake test was strongly positive, +389%, which is far above the critical level of +60%. A thorough medical examination for metastatic disease (including chest *x*-ray, liver function studies, and a liver scintigram) was negative. The clinical diagnosis was malignant melanoma of the choroid. Histological examination after enucleation confirmed that the tumour was a malignant melanoma of the epithelioid cell type which had already invaded halfway into the sclera.

Eight months after enucleation of the right eye the patient complained of blurred vision of his left eye. Within one day corrected visual acuity dropped from 6/6 to 5/60. Ophthalmoscopy revealed a rapidly spreading retinal detachment, becoming subtotal. At the lower periphery a tumour with a diameter of 10 mm, an elevation of 8 mm, and relatively little pigment was visible. Ultrasonography and a positive ^{32}P-uptake test of +181% supported the clinical diagnosis of malignant melanoma of the choroid.

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After enucleation the histological examination confirmed the diagnosis. The tumour contained mainly epithelioid cells which had penetrated through Bruch's membrane but had not invaded the sclera. The extensive medical examination was repeated. This time the chest *x*-ray tomogram showed 3 lesions indicative of metastases.

In subsequent months the general condition gradually deteriorated due to metastatic spreading. Nine months after enucleation of the second eye the patient died.

This patient was a member of a family in which the FAMMM syndrome occurred. This family has been studied extensively[4] (in the pedigree from that publication he is III–8). In an earlier report on inherited malignant melanomas[1] he appears as IV–16 of pedigree 2.

CASE 2

A 52-year-old man was referred because of a 4 D prominent tumour with the aspect of a choroidal melanoma, measuring 5 mm in diameter and located superior to the posterior pole. Corrected visual acuity was 0·6. Fluorescein angiography showed a pattern typical of choroidal melanoma; perimetry revealed an absolute scotoma at the site of the tumour. The 48-hour ^{32}P-uptake test was positive, +107%. In view of the clinical diagnosis of malignant melanoma of the choroid the eye was enucleated. On histological examination the tumour proved to be a spindle B cell melanoma of the choroid.

The medical history was significant in that a pigmented skin lesion on his arm had been excised 2 years previously. Examination in the Department of Dermatology (Professor D. Suurmond) revealed a pigmented spot at the margin of the scar resulting from the previous removal. After excision histological examination showed the tumour to be a cutaneous malignant melanoma (Clark III). Two pigmented lesions were excised from the skin of the back; on histological examination they proved to be benign naevi. Six years later the patient is still in good health. There is no family history of malignancies, but a medical examination of the family members was not carried out.

CASE 3

A 59-year-old woman was referred because of metamorphopsia, and the patient had noticed a small scotoma when playing tennis. The cause was a 2 D prominent tumour with a greyish, slightly pigmented aspect and located temporal to the posterior pole in the fundus of her right eye. Corrected visual acuity was 1·0. Perimetry revealed a small, absolute scotoma nasal to the fixation point. Fluorescein angiography showed a pattern typical of choroidal melanoma; the tumour was 5–6 mm in diameter according to ophthalmoscopic and ultrasonographic measurements. The 48-hour ^{32}P-uptake test was positive, +93%. Local irradiation was considered, but since the patient refused this treatment the eye was enucleated. On histological examination the tumour proved to be a spindle cell melanoma of the choroid. Seven years previously the patient's mother, aged 77 years, had been admitted to the ENT department of our hospital. She underwent surgery because of a large tumour in the nasal sinuses extending into all paranasal sinuses and into the left orbit. Complete removal of the tumour, which was found to be a malignant melanoma probably originating from the left ethmoidal sinus, was impossible. The patient died 8 months after the operation.

Discussion

Patients with hereditary forms of cancer may present a different clinical picture from that of patients with non-hereditary forms. The tumour may have an earlier age of onset and be bilateral, and the patient may have multiple primary cancers at different anatomical sites.[1–4] Patient no. 1 is most unusual as a case of bilateral choroidal melanomas and multiple primary cutaneous malignant melanomas, while a study of his family has revealed the presence of the FAMMM syndrome. This syndrome derives its name from the clinical characteristics of multiple naevi, which vary in size (many 10 mm or more in diameter) and which may number as many as a hundred or more in certain patients. The naevi may vary in hue between tan, brown, pink, and red, occasionally with a variegated pattern, and are localised primarily on the upper part of the trunk or extremities, but may occur anywhere on the body; they have characteristic histological features.[2 4] Patients with this syndrome are at risk of developing cutaneous melanomas and possibly also other primary malignancies.[1–4] The FAMMM syndrome is inherited as an autosomal dominant trait.

The additional presence of independent bilateral choroidal melanomas in patient no. 1 is very rare. The incidence of unilateral uveal melanoma is 1:70 000 to 1:100 000; thus bilateral occurrence of uveal melanoma must be very rare. Only 22 cases have been reported,[5–8] to which we add one more. Jensen[9] had no bilateral cases among his 295 melanoma patients. We found one in more than 250 patients.

The chance of the simultaneous but coincidental occurrence of primary cutaneous melanomas and a primary ocular melanoma in each of 2 patients (our cases 1 and 2) seems to be practically nil since these malignancies have an incidence of about 4:100 000 and 1:100 000 respectively.[10] In addition 4 other cases of this condition have been described. In two of these[11 12] the tumours developed in patients with the FAMMM syndrome, as we observed in our patient no. 1. In the other 2 patients[13 14] (like our patient no. 2) the development of skin and uveal melanomas was not associated with the FAMMM syndrome. However, Bellet *et al.*[12] suggest that the choroidal tumour described by Paton and Thomas[13] should be redesignated as a choroidal naevus according to the reclassification of choroidal melanomas.[15]

The occurrence of intraocular and cutaneous melanomas in different members of a family has only been described in 3 families. Turkington[16] mentions a brother and sister with an intraocular and a cutaneous melanoma respectively. Lynch and Krush[17] reported on 2 sisters, one with an intraocular and one with a cutaneous melanoma, and on a father and son with an intraocular melanoma and a melanoma of the skin respectively. We add one more family: patient no. 3 with a choroidal melanoma had a mother who succumbed to an ethmoidal melanoma. To this could be added our patient no. 1, since the family study revealed the presence of further malignant melanomas, atypical multiple moles, and other malignancies.

The frequency of the hereditary form of malignant melanoma of the skin was reported to lie between 0·4 and 12% of all melanomas depending on the intensity and mode of search. When intensive case finding was employed, 10·7% of 666 melanoma patients had a positive family history.[18] Reports of the familial occurrence of intraocular melanomas, on the other hand, have been very rare, but perhaps they have not yet received proper attention. Only 11 families have been reported with this most frequently occurring intraocular tumour developing in 2 family members.[18 19] Its occurrence in 3 successive generations has been reported only twice.[20 21] Lynch *et al.*[22] found that out of 45 patients with intraocular melanoma there was only one familial occurrence (in brother and sister). We observed no familial occurrence in over 250 patients with intraocular melanoma. In the 11 families reported the intraocular melanomas were not associated with skin melanomas. Moreover in 28 families with skin melanomas not a single case of intraocular melanoma was found.[23]

The few reported instances of familial intraocular melanoma are compatible with autosomal dominant inheritance; the FAMMM syndrome, in which skin melanomas may develop, also follows an autosomal dominant pattern of inheritance. It is not possible to state whether the genes involved are identical, are alleles, or are situated at different loci. The simultaneous presence of intraocular and skin melanomas in 3 individuals with the FAMMM syndrome[11 12] (including our own), which cannot be a coincidence as stated above, is good evidence for a single gene being responsible for both. This has also been suggested by Rodriguez-Sains.[24]

The presence of an intraocular malignancy in association with an extraocular malignancy is very unusual, since only 41 cases have been reported.[21 25 26] In cases of multiple primary malignancies involvement of the eye is very rare. Morgan *et al.*[25] reported on a patient with 3 primary malignancies, including an ocular tumour. Pheasant *et al.*[26] described a uveal melanoma as a fourth primary malignancy. Our patient no. 1 had 5 separate malignancies which may have been independent (although caused by a single gene defect): 3 skin melanomas and 2 choroidal melanomas. Ocular metastasis from a systemic melanoma, however, cannot be excluded. The data indicate that the risk that an additional tumour will develop in a patient suffering from a primary malignant uveal tumour is very small. In the case of patient no. 1, however, the existence of 4 malignancies should have led to careful follow-up of the remaining eye, as early detection of the melanoma in his second eye would perhaps have saved his vision by allowing time for irradiation treatment[27] or local excision[28] when the tumour was still small. Therefore ophthalmologists should be aware of the risk of development of new malignancies when treating a patient with an intraocular melanoma who has a positive family history or cutaneous signs of the FAMMM syndrome.

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British Journal of Ophthalmology, 1982, **66**, 234–239

Prostatic carcinoma metastatic to choroid

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SUMMARY Metastatic prostatic carcinoma of the choroid became clinically undetectable after orchidectomy and oestrogen administration. The choroidal tumour rapidly regressed over a 2-month period and clinically disappeared, with restoration of 6/6 vision from 6/60 and return of visual field. This dramatic response and lack of complications make hormonal manipulation the preferred mode of initial therapy in prostatic carcinoma metastatic to the choroid.

In 1872 Perls reported the first case of carcinoma metastatic to the choroid.[1] Since that time well over 400 cases have been reported.[2 3] The predominant sources of metastatic carcinoma to the choroid have been lung in men and breast in women.[2] There have been at least 7 reported cases of prostatic carcinoma metastatic to the choroid.[2 4–9]

This report describes a case of prostatic carcinoma metastatic to the choroid in which hormonal therapy caused complete clinical regression of the metastasis and full return of visual function. To our knowledge this response has not been previously reported with a choroidal metastasis from prostatic carcinoma.

Case report

A 54-year-old white male was referred to the Scott and White Clinic for evaluation of decreased vision in his left eye of 4 months' duration. His past medical history consisted of diabetes mellitus for two years treated with 10 units of insulin per day and chronic hypertension treated with a combination of reserpine, hydralazine, and hydrochlorothiazide. Review of systems revealed impotence, sacral pain, and urinary frequency.

Eye examination revealed a best corrected visual acuity of 6/6 right eye and 6/60 left eye. The positive physical findings were confined to the left fundus. A nonpigmented choroidal tumor was present temporally extending into the fovea and approximately 9 mm vertically by 6 mm horizontally (Fig. 1A). Very minimal subretinal fluid was associated with it. B scan ultrasonography showed a choroidal tumour with moderate internal reflectivity, no choroidal excavation, and about 5 mm in thickness (Fig. 2). Fluorescein angiography showed widespread hyperfluorescence due to defects of the retinal pigment epithelium but no distinct tumour circulation (Fig. 3A). Goldmann perimetry demonstrated an absolute visual field defect nasally in the left eye (Fig. 4A).

General physical examination was unremarkable with the exception of an enlarged, nodular prostate. On laboratory testing an acid phosphatase level of 21 IU/l (normal 0–6) and a prostatic fraction of 13 IU/l (normal 0–6) was noted. Chest *x*-rays revealed numerous nodular densities compatible with metastatic lesions. Prostatic needle biopsy confirmed grade 3 moderately well differentiated adenocarcinoma of the prostate (Fig. 5). No lesions were demonstrable on computerised axial tomography of the head. Bone scan revealed abnormal uptake in the axial skeleton, ribs, and entire left orbit (Fig. 6).

Over a period of a week the patient was treated with palliative cobalt-60 irradiation to painful bony lesions, transurethal resection of the prostate, and bilateral orchidectomy. In addition he was started on diethylstilboesterol 3 mg per day. Within 2 weeks the choroidal tumour had decreased to one-half its original size (Fig. 1B) and vision had improved to 6/15. In 4 weeks visual acuity improved to 6/6, and within 2 months the tumour was not clinically apparent (Fig. 1C). The visual field became almost

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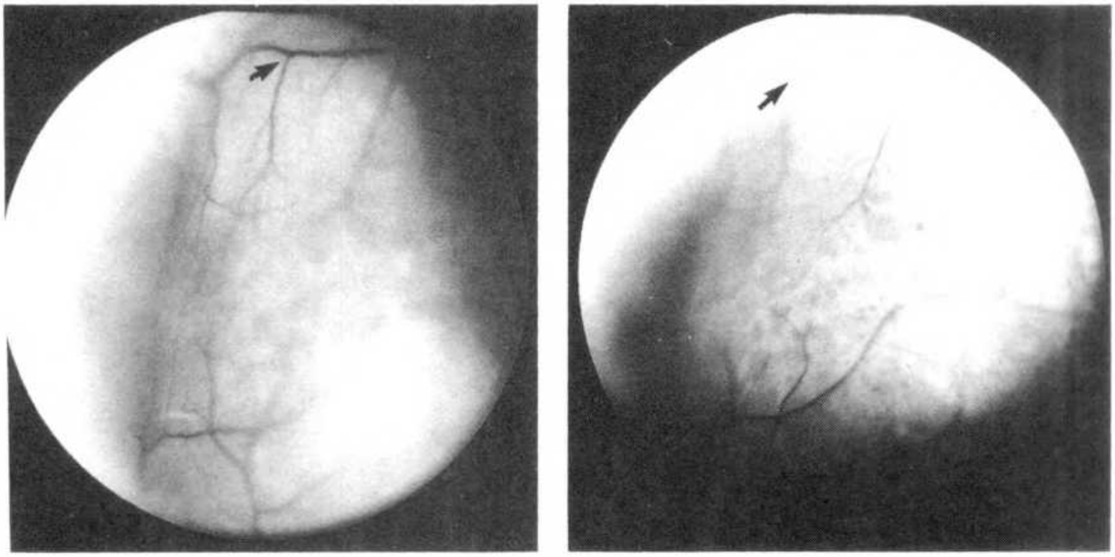
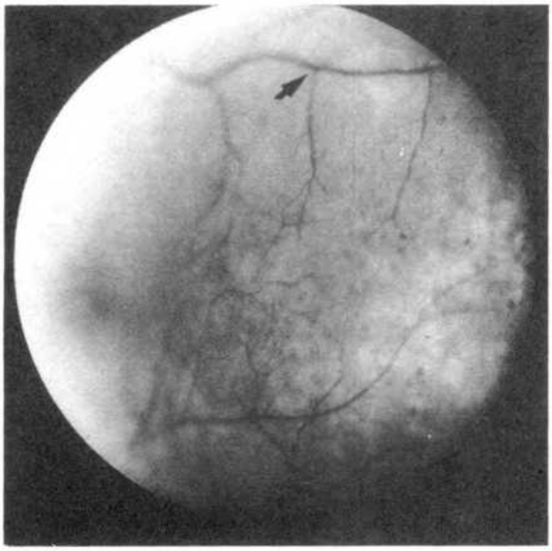


1A 1B



1C

Fig. 1 (A) *Tumour at left fundus at time of presentation.* (B) *After 2 weeks of hormone therapy.* (C) *After 2 months of therapy. (Arrow indicates same vascular landmark in each figure.)*

full (Fig. 4B) and the acid phosphatase level normal. The only evidence of the previous tumour was atrophy of the retinal pigment epithelium, which was prominent on fluorescein angiography (Fig. 3B). After 12 months of follow-up he is free of any ocular recurrence.

Discussion

Greenwood and Southard reported the first case of prostatic carcinoma metastatic to the choroid in 1903.[10] Since then at least 4 cases have been reported in the American and 3 in the European literature.[2 4-9] Several large series of metastatic choroidal tumours from various sites have included previously reported cases.[2 7 8]

The usual presenting symptom is decreasing visual acuity secondary to serous retinal detachment from choroidal metastasis; however, concurrent choroidal and optic nerve involvement has been reported.[9] Some of the reported cases received enucleation for relief of pain or diagnostic purposes. Others died

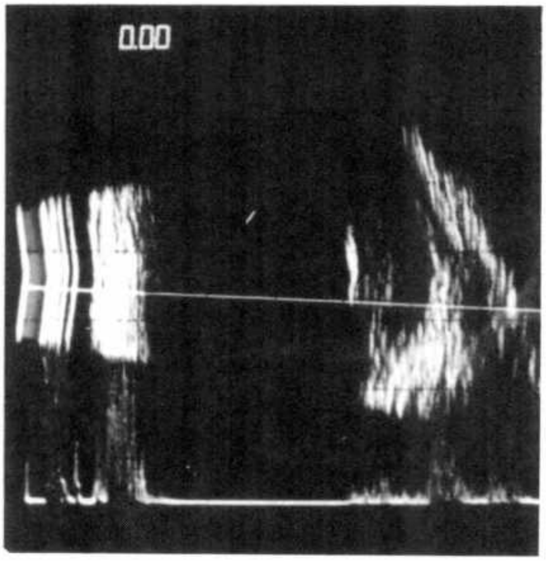
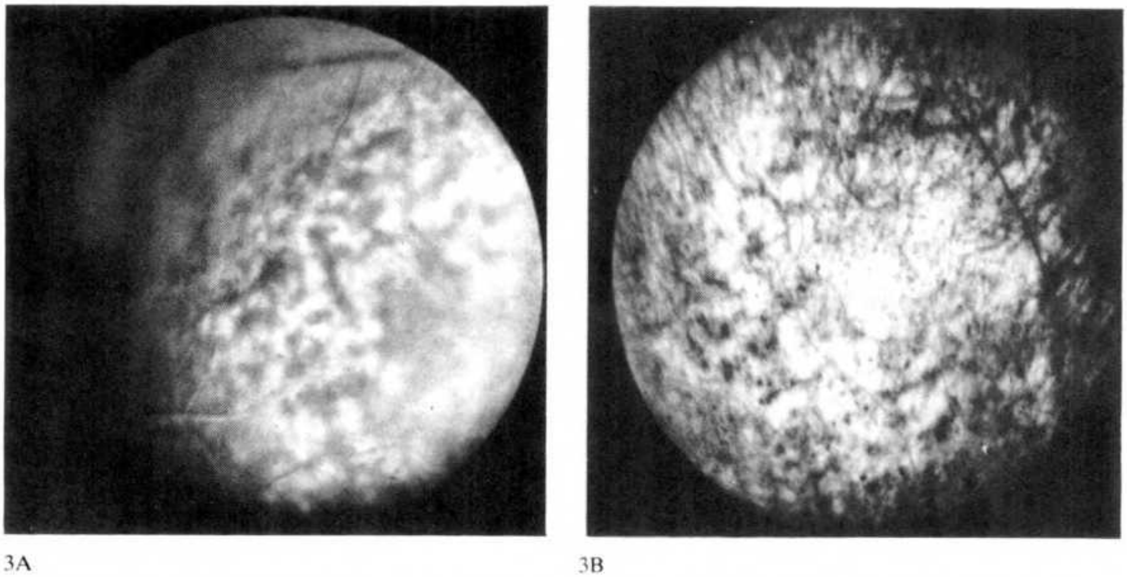


Fig. 2 *Combined A and B ultrasonogram showing tumour 5 mm in thickness with moderate internal reflectivity.*



3A

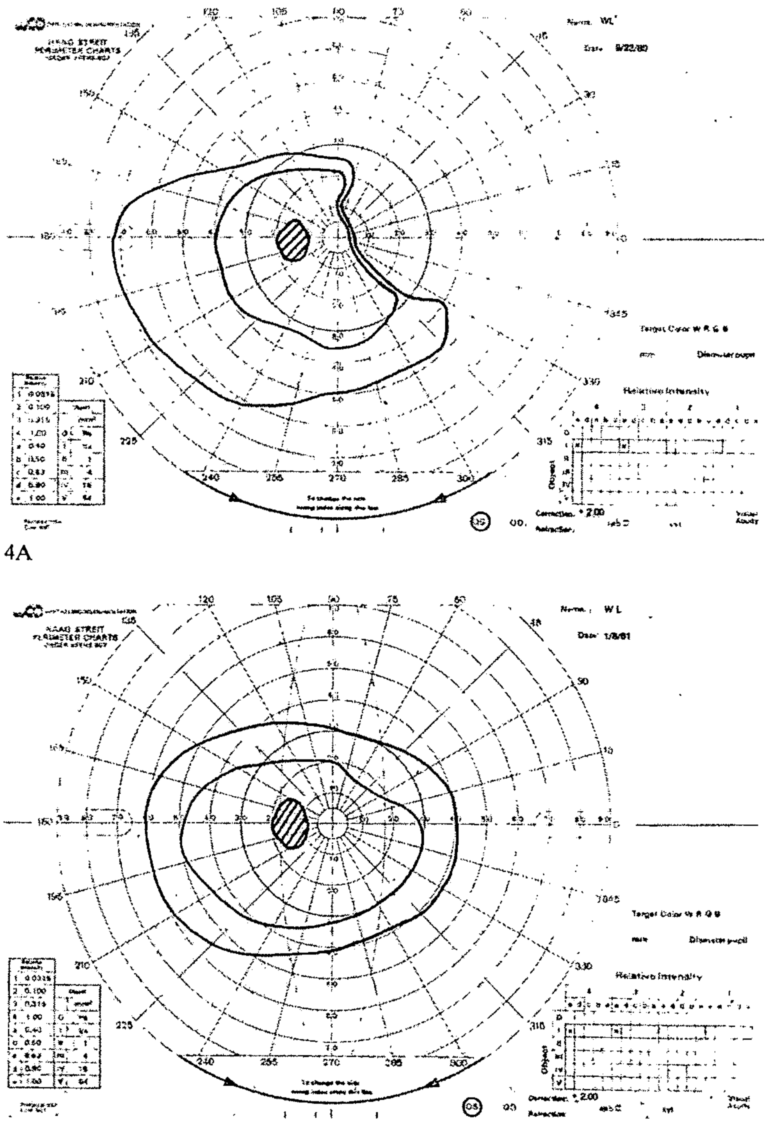
3B

Fig. 3 (A) *Fluorescein angiography showing hyperfluorescence due to window defects prior to treatment.* (B) *More extensive atrophy of the retinal pigment epithelium after tumour regression.*

before any ocular therapy was attempted. None of the reported cases were managed with hormonal manipulation.

Prostatic carcinoma metastatic to the choroid accounts for only 1·7% of all choroidal metastases in the series by Hart.[8] The incidence of choroidal metastases of all types is unknown, since no prospective studies have been done to answer this question.[11, 12] In a retrospective study[13] only 6 patients with choroidal metastases were found out of 8712 patients with neoplasms of all types.

The percentage of ocular metastases in those patients with prostatic carcinoma is also small. Many series do not even mention ocular metastases. One early series[14] of 100 necropsies of patients with metastatic carcinoma of prostatic origin included only



4A

4B

Fig. 4 (A) *Goldmann visual field of left eye at time of presentation.* (B) *After 4 months of therapy.*

one case of ocular involvement, the same case as Greenwood and Southard reported.[10]

Prostatic carcinoma can metastasise to the choroid by at least 2 routes. In those individuals with metastases in the lungs, as in our case, tumour emboli pass via the pulmonary circulation into the heart and aorta. They subsequently travel up the carotid arteries to the ophthalmic artery and into the ciliary vessels and uveal tract.

If no pulmonary lesions are present, prostatic or vertebral lesions may seed into Batson's plexus. In this way tumour emboli can bypass the pulmonary circulation and reach the cranial venous sinuses. From the cranial venous sinuses the emboli can reach the ophthalmic veins and vortex veins. Batson's plexus is valveless, and many reversals of flow are said to occur with changes in venous pressure secondary to changes in body posture and Valsalva manoeuvres.[15]

This case is unique in that all the patient's ocular symptoms and signs resolved with hormonal therapy. The physiological basis for hormonal therapy of metastatic prostatic tumours is well outlined by

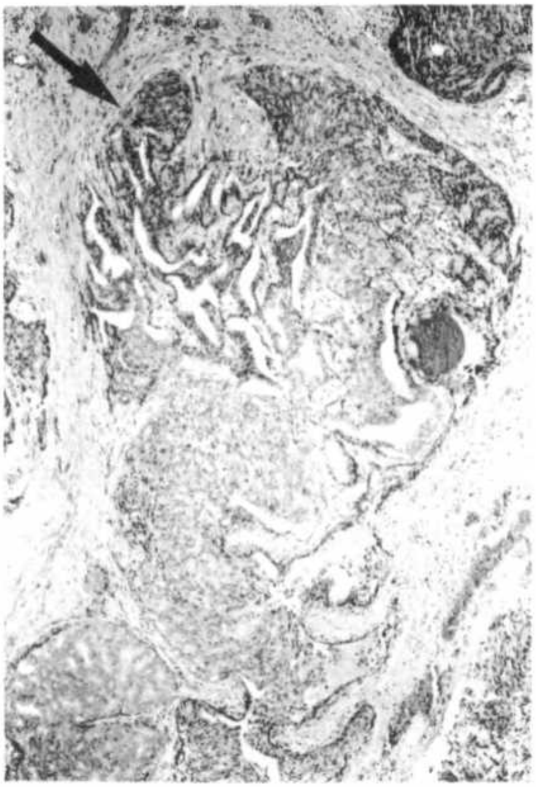


Fig. 5 *Needle biopsy of prostate showing grade 3 adenocarcinoma (arrow) (×70).*

Fig. 6 *Technetium-99 bone scan showing increased uptake in right globe (arrow), ribs, and pelvis at time of presentation.*

Walsh and is beyond the scope of this report.[16] Choroidal tumours derived from breast carcinoma have been shown to be responsive to hormonal manipulation.[17 18] The time course of resolution of ocular lesions was 2 to 3 months in these cases. A similar time course was noted in our case. Exophthalmos secondary to prostatic carcinoma to the orbit has also been shown to resolve with hormonal manipulation over a similar time course.[19–21]

According to Reese the goals of treating metastatic tumours to the choroid are preservation of vision and prevention of pain.[22–24] Carcinoma metastatic to the choroid has a poor prognosis, with life expectancy measured in months.[2 24] Radiotherapy has been the treatment of choice, since it may cause tumour regression and restoration of vision over 4 to 8 weeks.[3 25 26] Since hormonal manipulation is commonly used to treat widespread metastases from prostatic carcinoma, the effect of this form of therapy on choroidal metastases from the prostate should be observed before recommending radiation therapy.

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British Journal of Ophthalmology, 1982, **66**, 240–241

Visual disturbances during pregnancy caused by central serous choroidopathy

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SUMMARY Three patients had during pregnancy visual disturbances caused by central serous choroidopathy. One of them had a central scotoma in her first and second pregnancy. The 2 other patients had a central scotoma in their first pregnancy. Symptoms disappeared spontaneously after delivery. Except for the ocular abnormalities the pregnancies were without complications. The complaints can be misinterpreted as pregnancy-related optic neuritis or compressive optic neuropathy, but careful biomicroscopy of the ocular fundus should avoid superfluous diagnostic and therapeutic measures.

Central serous choroidopathy (previously called central serous retinopathy) is a spontaneous serous detachment of the sensory retina due to focal leakage from the choriocapillaris, causing serous fluid accumulation between the retina and pigment epithelium. This benign disorder occurs in healthy adults between 20 and 45 years of age, who present with symptoms of diminished visual acuity, relative central scotoma, metamorphopsia, and micropsia. Males are affected more commonly than females by at least 10 to one.[1] Most eyes have a complete visual recovery over a variable period of time. The cause of the condition is unknown.

Although this disease usually affects males, we have observed central serous choroidopathy in pregnant females. The course of symptoms in these patients made a causal relationship with pregnancy probable.

Case reports

CASE 1

A 34-year-old woman (gravida 2) noted visual blurring and a relative central scotoma in the left eye when she was 28 weeks pregnant. Ophthalmological examination was performed 10 weeks later, on 17 March 1981. Visual acuity was 6/5 in the right eye and 6/6 in the left eye. Indirect ophthalmoscopy and slit-lamp biomicroscopy of the fundus with a Goldmann contact lens showed a serous detachment of the neurosensory retina in the macular region of the affected left eye. Fluorescein angiography was not performed because of pregnancy. In her first pregnancy the patient had consulted an ophthalmologist on 13 June 1977 for exactly the same symptoms, which had disappeared spontaneously after delivery. Except during pregnancy the patient never had visual complaints.

Delivery was 5 days later. Without treatment the central scotoma and serous detachment disappeared within 2 weeks. Both pregnancies had been normal from the obstetrical point of view.

CASE 2

A 27-year-old woman (gravida 1) noted a relative central scotoma in her right eye when she was 20 weeks pregnant. Ophthalmological examination on 18 July 1980 disclosed a serous detachment of the sensory retina in the macular region of the right eye. The macular lesion was evident by the slit-lamp microscope and Goldmann contact lens, so fluorescein angiography was not performed in pregnancy. The visual acuity was 6/30 in the right eye after correction (S+2·0) of hypermetropia and 6/6 in the emmetropic left eye. Without treatment the serous detachment persisted during pregnancy.

After delivery the first ocular examination was performed on 6 March 1981. The visual complaints had disappeared, and visual acuity had returned to 6/6 without correction. There was no evidence of

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serous detachment of the sensory retina. The macula of the right eye showed a slight granularity of the pigment epithelium. The pregnancy had been uneventful from the obstetrical point of view.

CASE 3

A 32-year-old woman (gravida 1) noted blurred vision and central scotoma in her right eye when she was 32 weeks pregnant. Ophthalmological examination on 14 August 1980, one week after the initial symptoms, disclosed a serous detachment of the sensory retina in the macular region of her right eye. Visual acuity was 6/30 in the right eye and 6/6 in the left eye.

After delivery on 29 September visual complaints disappeared spontaneously. On 27 November 1980 ophthalmological examination disclosed visual acuity 6/6 in the right eye. There was still some metamorphopsia (Amsler grid), but the serous detachment had disappeared. The pregnancy had been normal from the obstetrical point of view.

Discussion

The occurrence of central serous choroidopathy in 4 pregnancies of these 3 patients, and the spontaneous recovery after delivery, suggested a causal relationship of the disorder and pregnancy. Chumbley and Frank[2] reported central serous retinopathy in a 34-year-old woman during 4 consecutive pregnancies, with remission after delivery or spontaneous abortion. The authors suggest that a hormonal agent, which increases in concentration during pregnancy, is one possible causative factor in this disease. However, since the disorder is more common in men, and usually unilateral, other systemic and ocular factors must play a role.

One of the changes in a normal pregnancy is an increase of plasma volume and total blood volume. Probably circulatory changes in the choriocapillaris can provoke central serous choroidopathy in predisposed eyes. The importance of the ocular factor is suggested by the fact that in consecutive pregnancies the relapse of central serous choroidopathy occurred in the same eye.

Fastenberg *et al.*[3] found predominantly abnormal choroidal vascular patterns in toxaemia of pregnancy, implicating choroidal vascular insufficiency as the basis for secondary retinal detachments seen in this complication. However, our patients had a normal pregnancy from the obstetrical point of view, without signs of toxaemia.

It is of the utmost importance to distinguish the correct causes of visual disturbances and field defects during pregnancy. In all cases a careful examination of the ocular fundus is necessary to exclude a retinal cause. The central scotoma can be misinterpreted as a result of optic neuritis. The association of optic neuritis and pregnancy has previously been suggested.[4–7] Visual disturbances during pregnancy have been reported as a result of the expansion of intracranial tumours (meningiomas, pituitary adenomas, and craniopharyngiomas) owing to hormonal changes.[5 8–11] As in our patients with central serous choroidopathy the spontaneous recovery of visual functions after delivery has been described in patients with intracranial tumours.[9–12]

If central serous choroidopathy is the cause of visual disturbances during pregnancy, its correct diagnosis may avert superfluous diagnostic and therapeutic measures.

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British Journal of Ophthalmology, 1982, **66**, 242–246

Dose response of oral timolol combined with adrenaline

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SUMMARY Oral timolol, a beta-adrenergic receptor blocker, was given in 5 different doses from 5 mg to 30 mg a day to 12 healthy volunteers in a double-blind cross-over trial. Adrenaline was instilled into one eye in each subject. Recordings of intraocular pressure during the trial suggested the presence of a dose-response relationship between the dose of timolol and the decrease of intraocular pressure. An analysis of the interaction of timolol and adrenaline showed that the adrenaline effect diminished linearly with increasing timolol dose, which finally made the combination less effective than timolol alone.

Most of the reports concerning the reduction of intraocular pressure by timolol maleate deal with topical timolol in clinical studies. To the best of our knowledge only one study reports on the reduction of intraocular pressure by oral timolol, and in that study[1] only a single dose of 5 mg oral timolol was used. Thus the effects on intraocular pressure of systemically administered timolol have not been fully investigated. Earlier investigations have given contradictory results, suggesting both additive and antagonistic effects of combining timolol and adrenaline.[2–4] As this combination avoids the disadvantages of miotics it could be a useful tool in the treatment of glaucoma. Earlier reports with oral beta-receptor blockers in the treatment of glaucoma[5–7] have encouraged the use of this alternative oral treatment when carbonic anhydrase inhibitors are unsuitable.

However, there has been no dose-response study on the subject of systemically administered timolol. This study was designed to investigate the effect on intraocular pressure of different doses of oral timolol and also the effect of simultaneously administered adrenaline.

Material and methods

The study was approved by the Ethical Committee of the Central Hospital Västerås, and followed the guidelines of the Tokyo-Helsinki convention. The trial was of randomised, double-blind, cross-over design (Fig. 1). Twelve volunteers, all females, age range 18 to 50 years, participated in the study. Timolol maleate tablets in 5 different strengths (2·5, 5, 7·5, 10, and 15 mg) were dispensed by the local pharmacy. Lactose was used in the placebo tablets. Adrenaline borate 1% eye drops (Eppy) and 0·9% saline as placebo drops were used to investigate the effect of adrenaline. One drop of placebo was instilled into one eye and one drop of adrenaline into the other, the distribution being randomised but balanced, so that 6 of the subjects received adrenaline in the right eye and the other 6 in the left.

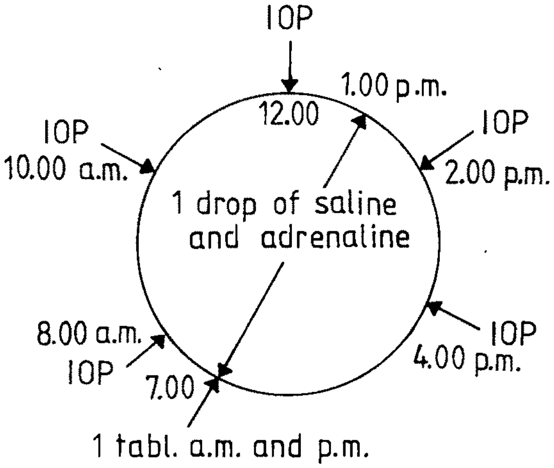

Fig. 1 *Design of the trial. Recordings of intraocular pressure and drug administration.*

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Table 1 *Mean intraocular pressure ±SEM with different doses of timolol: 0·9% saline in one eye and 1% adrenaline in the other. ΔE-P decrease of intraocular pressure following adrenaline drops. Each figure represents the mean of 110 recordings*

Oral dose	*Topical treatment*		*n*	*Δ E-P*
	Adrenaline drops (E)	*Placebo drops (P)*		
placebo	11·918±0·1661 $p<0·001$	12·764±0·1661 $p<0·001$	2×110	−0·845
5 mg	10·127±0·172	10·227±0·172	2×110	−0·1000
10 mg	10·409±0·161	10·436±0·161	2×110	−0·0273
15 mg	9·9000±0·1545	9·836±0·1545	2×110	0·0636
20 mg	9·818±0·1510	9·691±0·1510	2×110	0·1273
30 mg	9·773±0·1415	9·546±0·1415	2×110	0·2277

For each individual subject the adrenaline was instilled into the same eye throughout the trial. Six of the subjects were studied on Mondays and Tuesdays and the other 6 on Wednesdays and Thursdays. The trial was randomised, so that each subject received a different dose of timolol each week, and each week each dose was received by 2 subjects. At the start of the trial each subject was given one tablet at 7 p.m. The next day at 7 a.m. another tablet was given and at the same time the eye drops were instilled, one drop into each eye. From 8 a.m. the intraocular pressures were recorded 2 hourly until 4 p.m. (8 a.m., 10 a.m., 12 noon, 2 p.m., and 4 p.m.) with a calibrated Goldmann applanation tonometer, the recordings being made by the same investigator throughout the trial. At 1 p.m. one further drop of adrenaline and one of placebo were given. Another tablet was given at 7 p.m., and the whole procedure was repeated the following day.

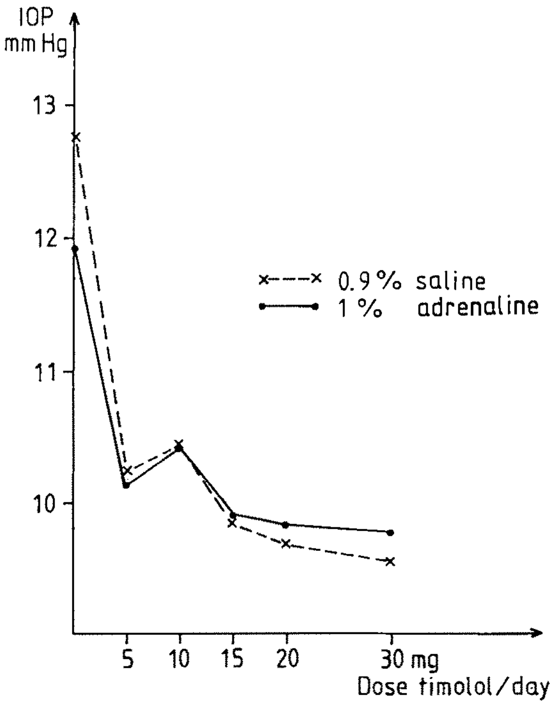

Fig. 2 *Dose-response curve of oral timolol with 0·9% saline drops in one eye and 1% adrenaline in the other eye. Every point represents the mean of 110 recordings.*

The results were analysed by Fisher's analysis of variance.

Results

During the third week one of the subjects developed bradycardia (45 beats/min) and had to leave the study. Her dose of timolol was 10 mg a day. The other 11 subjects completed the trial without any complications. The statistical analysis was based on a total of 1320 recordings of intraocular pressure (IOP).

Oral timolol used alone decreased the intraocular pressure significantly, $p<0·001$ (Table 1 and Fig. 2). In the full analysis of variance including both eyes treated with placebo drops and adrenaline the contrasts between eyes (reaction of IOP) and between timolol doses were not statistically significant, showing no further lowering of the IOP with increasing timolol doses.

However, when the half of the material (Table 2) in which no adrenaline was applied was analysed (Table 3), an increase in timolol dose was followed by a decrease in IOP values ($p<0·05$), which suggests a tendency towards a dose-response relationship.

An individual analysis of IOP responses revealed that one of the subjects reacted with an increase of IOP after adrenaline. This increase was significant

Table 2 *Timolol treatment without adrenaline, sum of recordings of IOP during day 1 and 2 (IOP totals) at different dose levels of timolol. Measurements in mmHg*

Dose: mg	*5*	*10*	*15*	*20*	*30*	
Individual no.	*IOP totals*					*Sum*
1	100	97	98	99	95	489
2	114	111	95	96	120	536
3	94	84	81	81	66	406
4	85	96	117	126	102	526
5	120	119	110	119	121	589
6	87	86	81	72	79	405
7	94	105	94	89	93	475
8	91	93	93	83	82	442
9	93	87	83	78	79	420
10	129	137	112	119	107	604
11	118	133	118	104	106	579
Total	1125	1148	1082	1066	1050	5471

Table 3 *Analysis of variance of the IOP: totals at different dose levels of timolol obtained in Table 2. DF=degrees of freedom. F=Fisher's variance quotient*

Analysis of variance	*Sum of squares*	*DF*	*Mean square*	*F*	*P*
Between individuals	11 048·91	10	1104·89	13·99	<0·001
Linear between doses	468·59	1	468·59	5·94	<0·05. (<0·02)
Nonlinear between doses	144·21	3	48·07	<1	NS
Experimental error	3158·00	40	$78{\cdot}95 = s_0^2$		
Total	14 819·71	54			

both with placebo tablets (p<0·01) and with different doses of timolol (p<0·001). This remarkable response prompted us to check this particular subject's reaction in a trial[3] of oral timolol and adrenaline performed one year previously. An analysis of variance showed (p<0·01) a significant inverse reaction to adrenaline in that trial also.

An analysis of the pure effect of adrenaline (placebo/placebo versus placebo/adrenaline) in the present trial would have shown, if the values of this particular subject had been excluded, that it usually caused a highly significant decrease of IOP (p<0·001). However, in order not to disturb the validity of the statistical analysis no values were excluded, and the tables thus include this inverse reaction.

When differences in IOP values were found between adrenaline- and placebo-treated eyes at the 5 dose levels of timolol, a linear correlation of the means emerged (Table 1, Fig. 3), which is suggestive of a gradual inhibition of the adrenaline effect with increasing timolol dose. An analysis of this correlation using the mean IOP differences gave p<0·001 by parametric methods and p<0·0083 by the non-parametric Kendall rank correlation test.

The statistical analysis showed no significant changes between the differences of tension in the eyes on different days. A slight heterogeneity was shown in the analysis of the importance of time of measurement and of the response of individual subjects, but no tendency could be shown.

Discussion

Several investigators have reported a dose-response relationship between the doses of oral beta blockers and the reduction of intraocular pressure (propranolol,[7] bupranolol,[8] timolol[3]). With topical treatment the relationship has been more thoroughly investigated (atenolol,[7] timolol,[9] metoprolol[10]), and Bonomi *et al.*[11] compared 9 different beta blockers.

This study shows that oral timolol lowers intraocular pressure when compared with placebo. A dose-response relationship seems to exist, but after 5 mg the further decrements of pressure with increasing dose are very small. A similar result was found in another study on timolol,[3] when 2 doses (5 mg and 20 mg) were used.

The interaction of beta blockers and adrenaline is controversial. Favourable results with topical timolol and adrenaline showing an additive IOP-reducing effect have been reported.[4] [12–15]

With the combination of topical atenolol and adrenaline Rushton[16] reported an additive hypotensive effect. Higgins and Brubaker[17] found that adrenaline and topical timolol had an additive effect on inhibiting the formation of aqueous humour, but found no significant change in the IOP.

On the other hand Phillips *et al.*[18] reported that the combination of local atenolol and adrenaline was less effective than atenolol alone, and Boger *et al.*[19] could not find any additive hypotensive effect of adrenaline in patients already receiving timolol drops. Goldberg *et al.*[20] reported that prior treatment with topical timolol for a week significantly diminished the reduction in IOP produced by adrenaline. In a

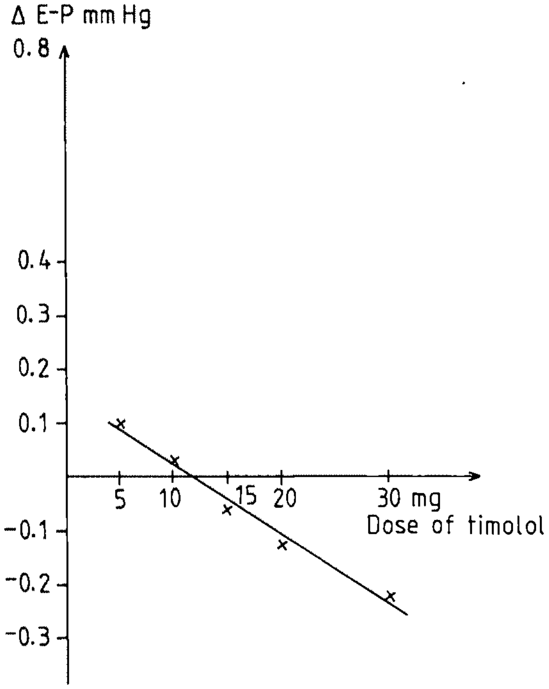

Fig. 3 *Δ E−P shows the differences in intraocular pressures between the eye treated with adrenaline and the eye treated with 0·9% saline with different oral doses of timolol.*

double-blind randomised cross-over study with healthy volunteers Öhrström and Pandolfi[2] demonstrated an antagonistic effect between topical timolol and adrenaline.

With respect to oral beta blockers, randomised double-blind cross-over trials have demonstrated an additive hypotensive effect of the beta-blocker–adrenaline combination.[2,3,21] In a prior trial with oral timolol,[3] in which doses of 5 mg and 20 mg were used, an additive effect was observed with the lower dose but an antagonistic one with the higher.

The present study (Fig. 3) shows that the effect of adrenaline diminishes linearly as the timolol dose is increased and that this finally makes the combination less effective than timolol alone.

As beta blockers act by competitive inhibition, a high oral timolol dose should provide a greater degree of beta blockade than a low dose. The doses used in this trial (5 mg–30 mg a day) could be expected to produce a beta receptor blockade ranging from weak to strong. The dose-response curve (Fig. 2) indicates that after 5 mg the additional effect of increasing the dose is very small, which is in agreement with Wettrell's observations on propranolol.[7]

Unfortunately there is no dose-response study comparing the IOP effects of different oral beta blockers. A systemic comparison of the beta blockade potency ratio, based on the inhibition of isoprenaline-induced tachycardia, showed timolol to be 6 times more potent than propranolol.[22] The timolol doses used in the present study should thus hypothetically correspond to doses of 30–180 mg propranolol a day. Wettrell[7] analysed the dose response for propranolol in doses 20–80 mg daily in ocular hypertension and showed a clear dose-response relationship. The mean IOP reduction from 20 mg propranolol was about 15–25%, and each doubling of the dose produced a further decrease of about 3–5%. The reduction was greater in the group with higher initial tension, a fact that has been observed by others.[23] In this study all the subjects were normotensive, with a mean baseline IOP of the untreated eye of 12·76±2·60 SD. After the smallest dose of timolol the pressure fell to values slightly over 10 mmHg. The episcleral venous pressure is probably only a few mmHg lower than this value, and thus a further suppression of the production of aqueous humour cannot possibly produce a lowering of the IOP, as it would then be below the episcleral venous pressure. Perhaps the dose-response curve would have had a different appearance if a sufficient number of ocular hypertensives had volunteered. Regrettably they did not.

The reduction of IOP by topical timolol has been shown by fluorophotometry to be due to a decreased formation of aqueous humour.[24] In a fluorophotometric study Townsend and Brubaker[25] showed that the immediate effect of adrenaline is to raise the facility of outflow and to increase the production of aqueous humour. A comparison between timolol and adrenaline shows that the IOP-reducing effect of topical timolol is significantly greater than that of adrenaline.[26]

There is no reason to believe that the basic mechanism producing the reduction of IOP differs between oral or topical timolol. Earlier observations of additive effects with low timolol doses and antagonistic effects with high timolol doses,[3] and the finding of this trial that increasing the timolol dose decreases the effect of adrenaline, can be explained if a low dose of timolol combined with adrenaline decreases aqueous humour production and increases the facility of outflow, while a high dose of timolol still produces a decrease of aqueous humour but blocks the adrenaline-mediated increase of facility. A similar theory is proposed by Thomas and Epstein[15] based on a study of the interaction of topical timolol and adrenaline showing a transient additive effect. The simultaneous stimulation by adrenaline of aqueous humour production would explain why a high dose of timolol combined with adrenaline is less effective than timolol used alone.

Since the beginning of the last decade oral beta receptor blockers, usually propranolol, have been used in the treatment of glaucoma.[5,6,27,28] This use of oral beta blockers is controversial and beyond the scope of the present discussion. However, when a patient with arterial hypertension and glaucoma needs treatment for both diseases, an oral beta blocker seems to be the drug of choice. The results of this study on healthy volunteers suggest that there are no benefits in using high doses of oral beta receptor blockers in the treatment of glaucoma.

Thanks are due to Dr Claus Rerup, University of Lund, for statistical analysis and planning.

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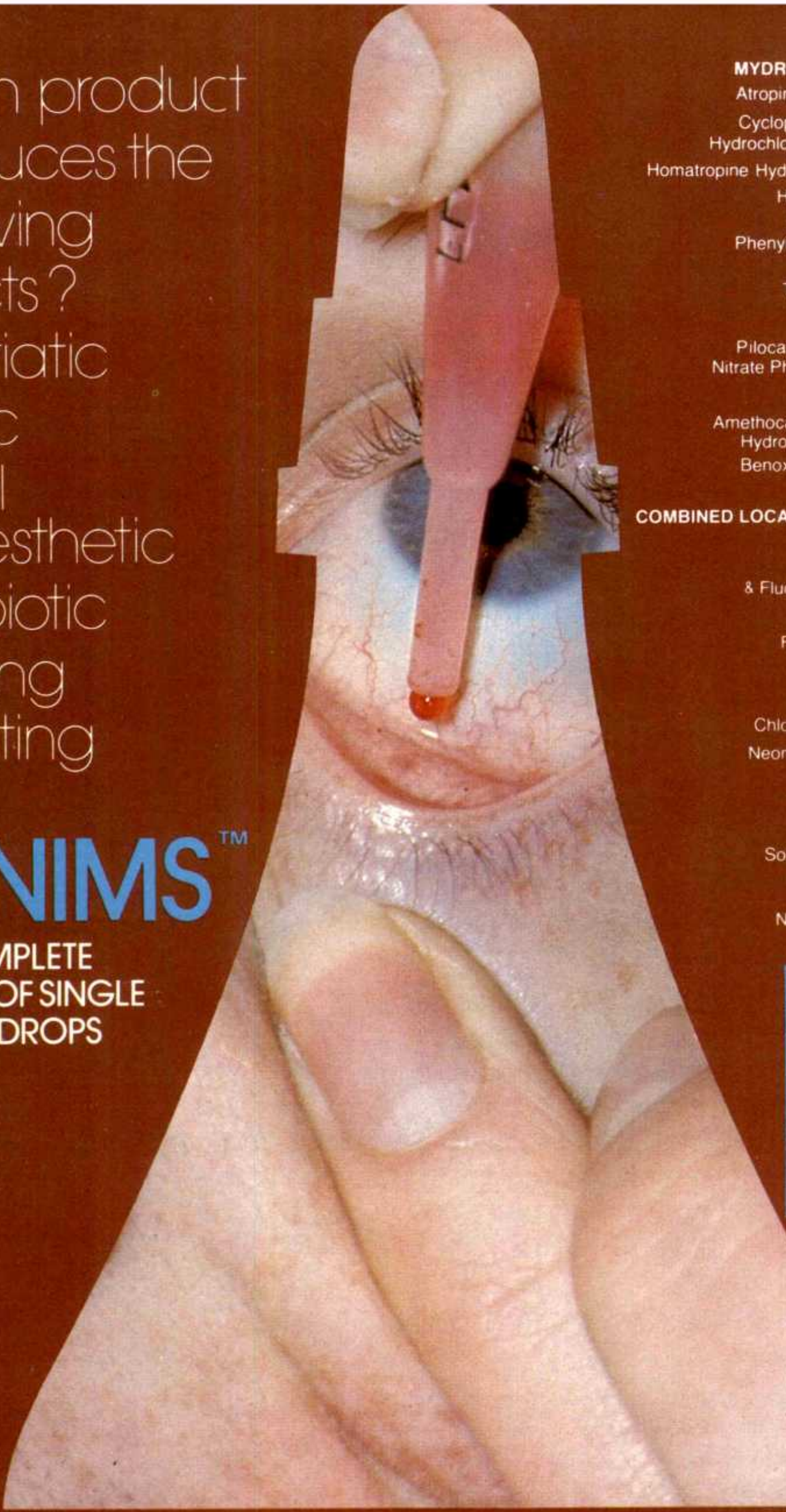

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British Journal of Ophthalmology, 1982, **66**, 247–249

Adrenaline 1% combined with guanethidine 1% versus adrenaline 1%: a randomised prospective double-blind cross-over study

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SUMMARY The hypotensive effect of a combination of guanethidine 1% with adrenaline 1% was compared with adrenaline 1% alone on the eyes of 20 patients with ocular hypertension in a randomised double-blind cross-over trial. The patients received 8 weeks of treatment with each preparation. A significant increase in the hypotensive effect was found by adding guanethidine 1% to adrenaline 1%. This hypotensive effect was maintained over the 8-week period of the trial.

Paterson and Paterson[1] introduced clinicians to the potentiating effect of adding guanethidine to adrenaline. Dose dilution studies suggested that a ratio of guanethidine 5:1 adrenaline was most effective. As a result different strengths of guanethidine with adrenaline were formulated; initially concentrations of 5:1 and then 5:0·5 and 3:0·5 were used. These strengths caused an appreciable incidence of side effects. Later Nagasubramanian and others[2] demonstrated that adrenaline 0·2% with guanethidine 1% had a sustained hypotensive effect. However, double-blind studies showed that this lower concentration did not have a greater hypotensive effect than 1% adrenaline alone, while the incidence of side effects was approximately the same.[3] More recently guanethidine 1% with adrenaline ½% was shown to have a greater hypotensive effect than adrenaline 1% without producing a greater incidence of side effects.[4] It seemed worthwhile, therefore, to see whether a further increase in the hypotensive effect could be obtained by combining guanethidine 1% with adrenaline 1%, and to see whether patients easily tolerated this combination.

Patients and methods

Twenty ocular hypertensive patients were drawn from the glaucoma clinic at Moorfields Eye Hospital, High Holborn. The basis of the study was explained and informed consent obtained.

The study design was as follows:

(1) An initial 7-day washout period off all antiglaucoma treatment (where necessary).

(2) Twice-a-day instillation of coded sympathomimetic preparation prepared and dispensed by the Moorfields Eye Hospital Pharmacy.

(3) Intraocular pressures were measured before treatment, and then at 1, 3, and 8 weeks after starting treatment on the first preparation. Intraocular pressures were measured at the same time of day. Care was taken to ensure that a repeatable intraocular pressure was obtained; the right eye was always measured first.

(4) At the end of the first 8-week period there was a further washout period lasting 7 days without any hypotensive therapy.

(5) The alternative coded sympathomimetic treatment was dispensed and the procedure repeated for a further 8 weeks as in no. 3 above.

(6) Throughout the study the patients' subjective comments were noted, as were observations of conjunctival hyperaemia, alterations in visual acuity, and ocular irritation.

Results

Twenty patients entered the trial. Seven patients could not complete one or other half of the trial. Each patient who wished to withdraw was restarted on his normal antiglaucoma treatment (where applicable) and re-entered the study at the time of the prescribed second washout period. After this period they were started on the alternative sympathomimetic preparation. One patient failed to re-enter the study.

Only two patients failed to complete both halves of

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Table 1 *Analysis of the paired results for each eye: Student's t test*

Comparison of pretrial washout IOP with IOP on adrenaline

Week	*I*	*III*	*VIII*
Mean IOP fall (mmHg)	(x̄)=1·89 mmHg SD=3·33 n=19 eyes t=2·47 p=<0·05	x̄=1·89 SD=2·59 n=19 t=3·18 p=<0·01	x̄=0·79 SD=2·14 n=19 t=1·61 p=>0·10

Comparison of pretrial washout IOP with IOP on guanethidine and adrenaline

Week	I	III	VIII
Mean IOP fall (mmHg)	(x̄)=3·17 SD=4·09 n=19 eyes t=3·38 p=<0·005	x̄=4·46 SD=4·31 n=15 t=4·01 p=<0·002	x̄=4·78 SD=4·16 n=15 t=4·45 p=<0·001

the trial. Three patients completed the adrenaline half but not the combination-drop half, while one patient completed the combination-drop but not the adrenaline half of the trial. In each case withdrawal was caused by intolerance to the drug in question. No patient was withdrawn because of high intraocular pressures.

Of the 20 patients entered one failed to complete even one half of the trial. Analysis has therefore been restricted to the 19 remaining patients. The intraocular pressures for the right eye are tabulated.

The mean pretrial washout IOP was 23·38 mmHg, SD 4·68.

The hypotensive effect of adrenaline alone and in combination with guanethidine has been set out in Table 1. The comparison has been made with the pretrial washout IOP. A comparison of the hypotensive effect of the 2 drugs has been set out in Table 2. Table 3 lists the noted side effects.

Table 2 *Comparison of IOP fall on adrenaline with IOP fall on guanethidine with adrenaline; shown as the extra hypotensive effect of guanethidine and adrenaline. Analysis of paired results by Student's t test*

Week	*I*	*III*	*VIII*
Mean extra hypotensive effect (mmHg)	(x̄)=1·61 SD=3·16 n=18 t=2·16 p=<0·05	x̄=1·80 SD=2·0 n=15 t=3·49 p=<0·005	x̄=3·33 SD=4·40 n=15 t=2·93 p=<0·05

Table 3 *Side effects*

Symptom	*No. of patients*	
	Guanethidine and adrenaline	*Adrenaline*
Headache/brow ache	4	1
Red eye	7	2
Burning	0	0
Ptosis	0	0
Ocular pain	1	0
Blurred vision	2	1

Discussion

The results presented here show that by adding guanethidine 1% to adrenaline 1% there is a marked and sustained increase in the hypotensive effect in the ocular hypertensive patients studied. This effect lasted for the full 8 weeks of the trial. There was an

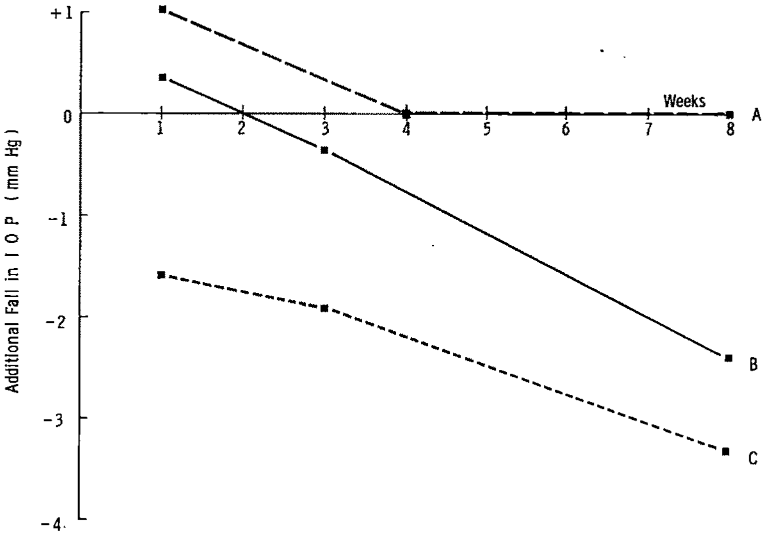

Fig. 1 *Comparison of the hypotensive effect of varying combinations of adrenaline combined with 1% guanethidine with adrenaline 1% alone. This has been recorded as the pressure difference between the different combination drops and adrenaline 1% alone for 3 different studies, for each study at 1, 3, or 4, and 8 weeks of treatment. There was a significant difference (p<0·05) between the intraocular pressures recorded on treatment with adrenaline 1% alone compared with varying strengths of the combination drops as follows: preparation A, week 1; B, week 8; C, week 1, 3, and 8. A=adrenaline 1/4%; B=adrenaline 1/2%; C=adrenaline 1%.*

increase in the side effects seen with the combination drop. However, not every patient intolerant of adrenaline was going to be intolerant of the combination drop and vice versa. Three-quarters of the patients found that the guanethidine and adrenaline drop was easily tolerated for the duration of the trial.

Further analysis of the results that were obtained by Murray *et al.*,[4] who conducted similar double-blind prospective studies, allowed a comparison of the additional hypotensive effect of adding guanethidine 1% to various strengths of adrenaline (¼, ½, or 1%) compared with adrenaline 1% alone. This analysis may be seen in Fig. 1. It will be seen that combining adrenaline 0·25% with guanethidine gives a combination drug of equivalent hypotensive effect to adrenaline 1% alone. Combining adrenaline ½% with guanethidine 1% gives a combination drop which by the eighth week of the trial gave significant extra hypotensive effect on the patients studied. However, the combination of adrenaline 1% with guanethidine 1% gave an immediate and sustained increased hypotensive effect when compared with adrenaline 1% alone and appeared the most potent hypotensive combination of the 3.

CONCLUSION

From this study it is suggested that combining guanethidine 1% with adrenaline 1% gives a useful antiglaucoma preparation which has a greater hypotensive effect than adrenaline 1% alone and also than weaker adrenaline concentrations combined with 1% guanethidine. Approximately 25% of the patients studied in this trial were not prepared to tolerate it for the 8-week period. This was a slightly greater number than those who were not prepared to tolerate adrenaline alone. However, the remaining patients were happy to use it in the long term. It is suggested that those patients with an inadequate hypotensive response to adrenaline alone could well benefit by being changed to a combination of adrenaline 1% with guanethidine 1%.

We thank Hugh Donovan for advice and help with the statistical analysis, and Kay Mills for secretarial help.

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British Journal of Ophthalmology, 1982, **66**, 250–252

Simultaneous trabeculectomy and cataract extraction

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SUMMARY A combined trabeculectomy and cataract extraction was performed on 46 eyes of 39 patients. The average follow-up period was of 27 months. The intraocular pressure remained controlled without the need of postoperative medication in 33 eyes (71·74%); 12 eyes (26·09%) needed further medical treatment; and in one eye the pressure remained uncontrolled and further surgery was necessary. After surgery the visual acuity improved considerably and the complications were few. The combined procedure has many advantages. The patient is cured by one surgical procedure, his visual acuity improves, his intraocular pressure is reduced to normal, and he is relieved from the need for medication postoperatively. By a single stay in hospital and by reducing the number of postoperative medical routine controls the expenses are reduced considerably. Owing to these advantages the combined procedure deserves to be considered in cases of glaucoma and cataract.

Opinions on the treatment of a cataract in an elderly patient with glaucoma differ from one author to another. According to some authors the cataract extraction alone makes the intraocular pressure (IOP) normal.[1] Others believe that the cataract extraction alone renders the control of glaucoma more difficult[2] and the lens extraction seldom relieves a coexisting glaucoma.[3] Different combined surgical methods have been recommended,[4–7] and when trabeculectomy took over the leading role[8] European,[9–11] Japanese,[12] and American surgeons[2 13] recommended a combined trabeculectomy and cataract extraction.

From 1977 to 1980 a combined trabeculectomy and cataract extraction was performed in our department on 46 eyes. The present study discusses the results, indications, and advantages of this procedure.

Material and methods

Since 1977, 46 eyes of 39 patients have undergone a combined trabeculectomy and cataract extraction. The age, sex, and follow-up period, the preoperative recordings, the indications, the results of measuring the intraocular pressure (IOP) and visual acuity, and the complications are shown in Tables 1, 2, 3, 4, 5, 6, and 7 respectively.

Surgical method. A limbus-based conjunctival flap, a scleral 3×4 mm trapdoor flap, trabeculectomy and peripheral iridectomy, enlargement of the corneoscleral incision, lens extraction by cryosurgery, suturing of the wound by 8–0 virgin silk sutures, and instillation of 1% atropine drops were carried out.

Patients. The main age group was between the 7th and 8th decade, the follow-up 12–42 months, average 27 months (Table 1). The preoperative findings are shown in Table 2. Thirty-eight patients had open- and 8 had narrow-angle glaucoma. Glaucomatous excavation was present in 22 eyes; the fundus was normal in 13 eyes; and because of a fixed miotic pupil the fundus findings were invisible in 11 eyes. Visual field defects were found in 14 eyes; 4 of them had tubular fields. The visual fields were normal in 8 and unknown in 24 eyes.

Table 1 *Age, sex, and follow-up period (46 eyes of 39 patients)*

Age:	*50–60 yr*	*60–70 yr*	*70–80 yr*	*Over 80 yr*	*Total*
No.:	3	7	27	9	46
Sex:	29 Females	17 Males			
Follow-up period: 12–42 months, average 27 months					

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Table 2 *Preoperative recordings*

	No. of eyes
Kind of glaucoma	
Open angle	38
Narrow angle	8
Fundus	
Glaucomatous excavation	22
No excavation	13
Unvisible	11
Visual fields	
Defects	14
Normal	8
Unknown	24
IOP	
Controlled without medication	0
Controlled by medication	22
Uncontrolled	24

Treatment. All the patients received antiglaucomatous treatment preoperatively. 'Maximal medication' means frequent and various kinds of topical and systemic antiglaucomatous medication.

The IOP was controlled by medication in 22 eyes and uncontrolled in 24 preoperatively. By 'controlled' we mean an intraocular pressure below 21 mmHg at all times round the clock. By 'uncontrolled' we mean an intraocular pressure over 24 mmHg, significant diurnal variations, and evidence of a damaging effect of the increased pressure on the eye.

The indications for a combined procedure (Table 3) were uncontrolled glaucoma and cataract in 24 eyes and controlled glaucoma and cataract in 22 eyes. In the uncontrolled glaucoma group the IOP was over 24 mmHg, with significant diurnal variations. The controlled glaucoma group included patients with increasing visual field defects (8 eyes), aphakia and glaucoma, or glaucoma surgery, in the fellow eye (4 and 8 respectively). In 17 eyes a central cataract and maximal miosis handicapped the patient.

Table 3 *Indications for a combined procedure*

		No. of eyes
1.	Uncontrolled glaucoma and cataract	24
2.	Controlled glaucoma and increasing visual field defect	8
3.	Aphakia and glaucoma in the fellow eye	4
4.	Glaucoma surgery in the fellow eye	8
5.	Controlled glaucoma central cataract and maximal miosis	17

Table 4 *Postoperative IOP*

	No. of eyes	*Percentage*
Controlled without medication	33	71·74
Controlled by medication	12	26·09
Uncontrolled	1	2·17
Total	46	100

Forty-three eyes had an intracapsular and 3 eyes an extracapsular lens extraction (one planned and 2 unplanned extracapsular extractions). The lens was extracted through a round pupil in 29 eyes; in 17 eyes an iridotomy was necessary in order to facilitate the extraction. In 17 eyes a synechiolysis was performed, and 2 eyes had vitreous loss.

Results

The results of operation are shown in Table 4, and compared with the preoperative readings in Table 5.

Table 5 *Comparison between the preoperative and postoperative IOP results*

	No. of eyes and percentage	
	Preoperative	*Postoperative*
Controlled without medication	0	33 (71·74%)
Controlled by medication	22 (47·8%)	12 (26·09%)
Uncontrolled	24 (52·2%)	1 (2·17%)
Total	46 (100%)	46 (100%)

Table 6 *Visual results*

6/6–6/10	*6/15–6/20*	*6/30–6/60*	*Less than 6/60*	*Total*
16	17	6	7	46

Table 7 *Postoperative complications*

Early	*No. of eyes*	*Late*	*No. of eyes*
Hyphaema	4	Post. synechiae	5
Shallow anterior chamber	3	Lens residua	1
Choroid detachment	3	Vitreous haemorrhage	1
Vitreous haemorrhage	2	Staphyloma	1

Thirty-three eyes had a controlled IOP without the need of medication, 12 eyes needed medication postoperatively, and in one eye the pressure remained high and further surgery was necessary.

A visual acuity (Table 6) of 6/6–6/10 was achieved in 16 eyes, 6/15–6/20 in 17 eyes, 6/30–6/60 in 6 eyes, and less than 6/60 in 7 eyes. There was complete atrophic glaucomatous excavation in 2 eyes, severe macular degeneration in 3 eyes, vitreous haemorrhage in one eye, and lens residua in one eye. These were the results following one surgical procedure.

The complications are shown in Table 7. The early complications were hyphaema (4 eyes), shallow anterior chamber (3 eyes), choroidal detachment (3 eyes), and vitreous haemorrhage (2 eyes). The late complications were posterior synechiae (5 eyes), lens residua (one eye), vitreous haemorrhage (one eye). An unusual complication developed in one eye: the IOP remained uncontrolled and a staphyloma developed at the corneoscleral section in the upper nasal quadrant. The patient underwent further surgery and the IOP became normal, but the visual result was poor owing to complete glaucomatous excavation.

Discussion

The combined operation of trabeculectomy and cataract extraction is not a popular procedure for several reasons. Some believe that the lens extraction alone can control the postoperative IOP,[1] that the control of the IOP is of a temporary character,[14] or that the combined procedure carries a high surgical risk[13] and severe complications.[15]

In all our patients except one the IOP remained controlled over a long period of time; 33 eyes did not need medication postoperatively (71·74%). As Witmer[3] stated, the extraction of cataract seldom relieves a coexisting glaucoma, and all eyes with this disorder need medical treatment. When an aphakic glaucoma develops, it is difficult to manage, the uncontrolled IOP is followed by a deterioration of the ocular function, and therefore even heroic measures have been suggested.[16] The complications in our cases were few and of a temporary character, and in our opinion, as in the opinion of others,[13] the combined procedure is no more traumatic than an ordinary cataract extraction.

Most of our patients were in the 7th and 8th decades, and most of them enjoyed good results from this procedure. Their visual acuity improved considerably, their IOP became normal, and only a few needed medication. In addition most of them feel a relief from routine administration of drops and routine and repeated medical control. The advantages of this procedure are not only medical but also financial: a single operation cuts the expenses considerably. Because of good visual results, the long-lasting control of the IOP, and the few complications the combined procedure is to be considered in patients with glaucoma and cataract.

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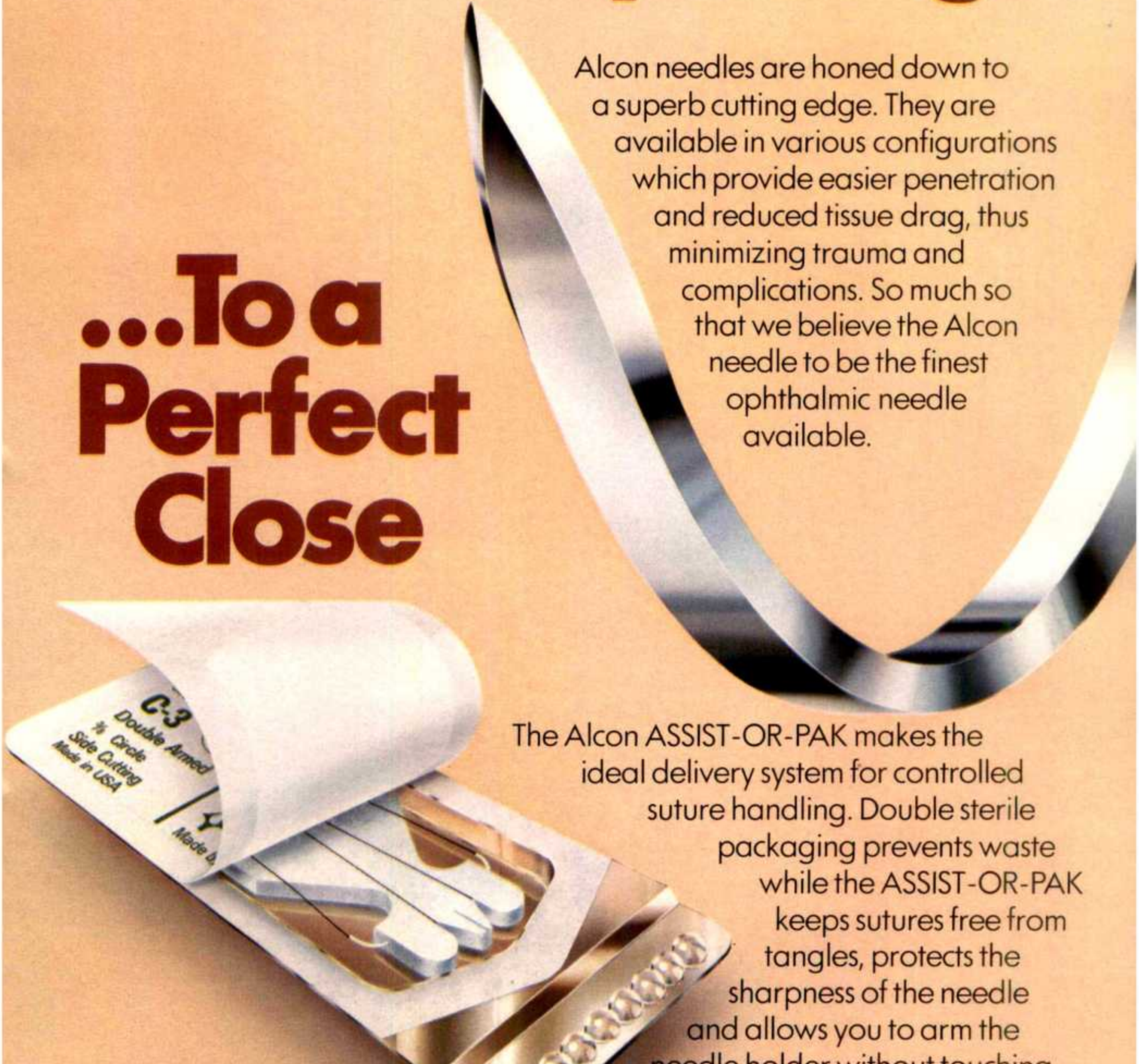

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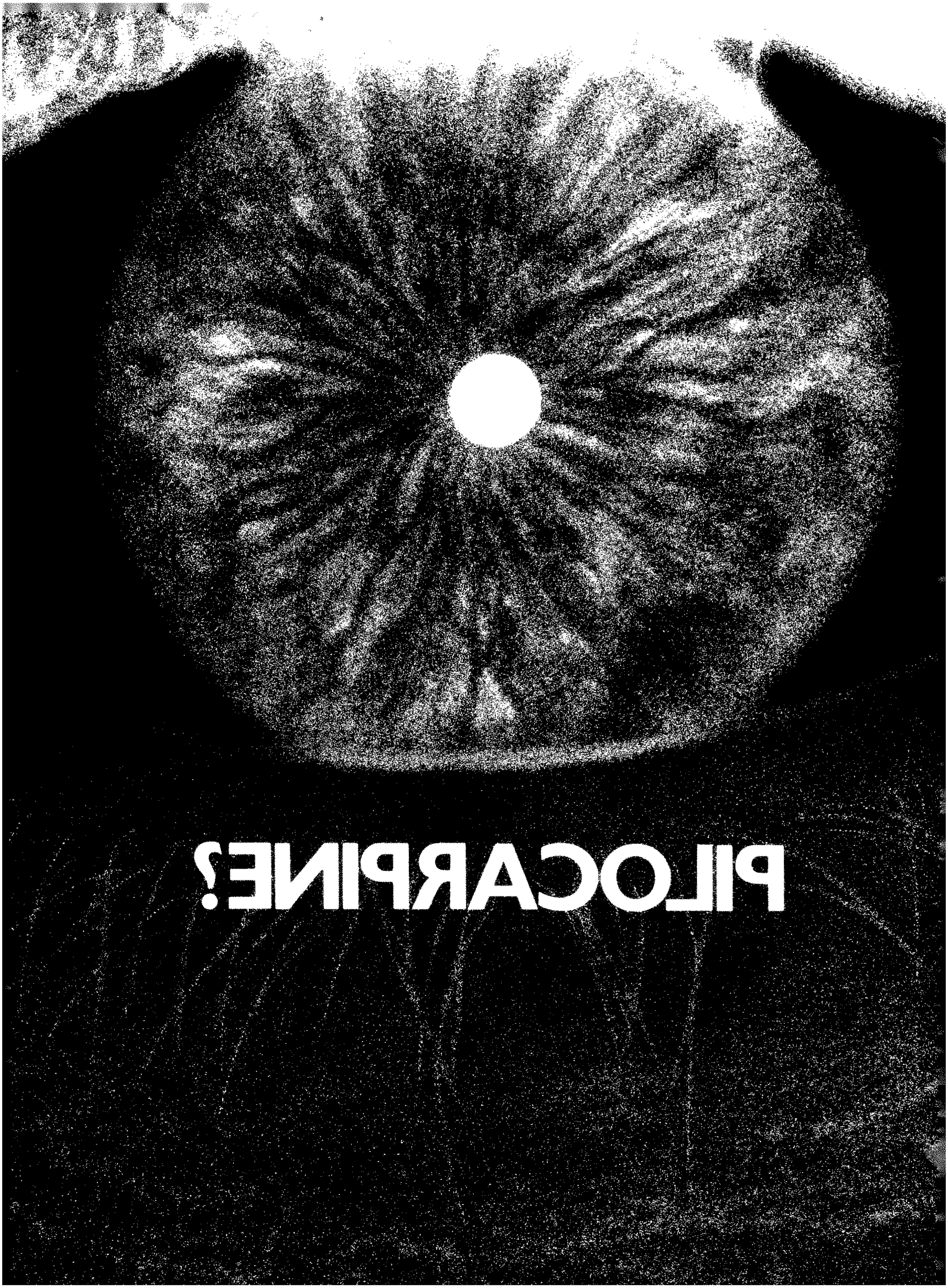
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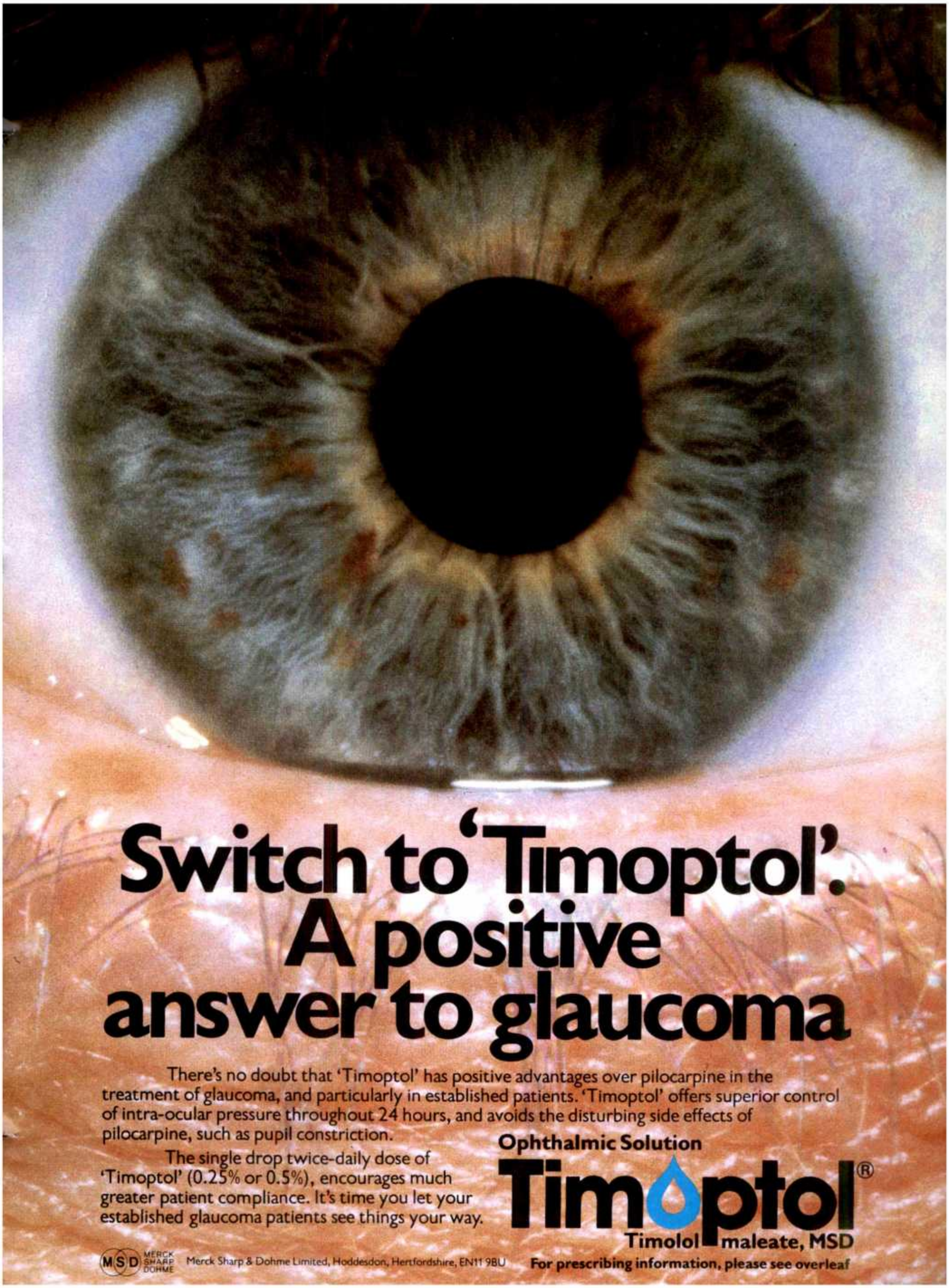

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British Journal of Ophthalmology, 1982, **66**, 253–257

An unusual extraocular muscle anomaly in a patient with Crouzon's disease

M. SNIR, E. GILAD, AND I. BEN-SIRA

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SUMMARY A 29-year-old female suffering from Crouzon's disease was admitted to hospital with retinal detachment in the right eye. At operation agenesis of 4 extraocular muscles (superior and inferior recti and obliquus) was found, together with abnormal insertion of the 2 horizontal muscles. The same extraocular muscular abnormalities were found in the left eye. We suggest here a new surgical treatment in such cases and discuss the reasons for the limitation of ocular motility in such cases.

Crouzon's disease is a rare birth defect[1,2] which in most instances is inherited as an autosomal dominant trait without complete penetrance.[1-3] Craniofacial dysostosis is characterised by bone and eye abnormalities. The bone defects include shallow orbits, protuberant frontal region, hypoplasia of maxilla, mandibular prognathism, enlargement of nasal bone and a beaklike nose, cleft palate, a high-arched palate, and dental malformation.[1,3-7]

The physical characteristics of Crouzon's disease vary considerably from case to case, but they are essentially the result of premature synostosis of cranial sutures; the sphenozygomatic suture plays an important role in the disease. This premature fusion is responsible for many secondary changes in the basic brain and eye development.[2,4,8-11]

Ocular manifestations include: exophthalmos, sometimes with luxation of the globe, obliquity of the palpebral fissures, ptosis, hypertelorism, optic atrophy, divergent strabismus, nystagmus, iridic and choroidal colobomas, and congenital cataract.[1,3-7,11-16] There may be interesting and irregular abnormalities connected with this malformation. These include hypoplasia of orbital margins, anomalous lacrimal passages, and absence of some extraocular muscles.[1,11,17]

The present report describes a patient with craniofacial disease and bilateral agenesis of 4 extraocular muscles—the superior and inferior recti and obliquus muscles. A special surgical procedure was used to prevent spontaneous luxation of the eyes and also to reduce the proptosis.

Correspondence to Dr M. Snir.

Case report

A 29-year-old female known to be suffering from Crouzon's disease (Fig. 1) was admitted to hospital with retinal tears and subtotal detachment in the right

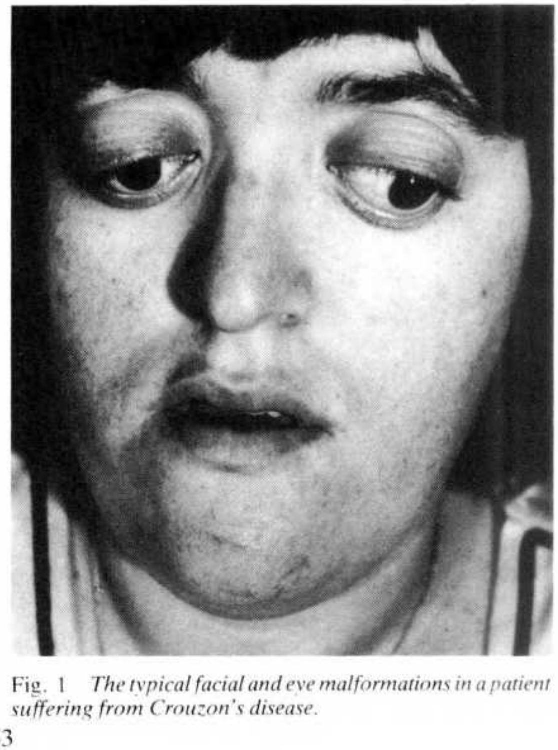

Fig. 1 *The typical facial and eye malformations in a patient suffering from Crouzon's disease.*

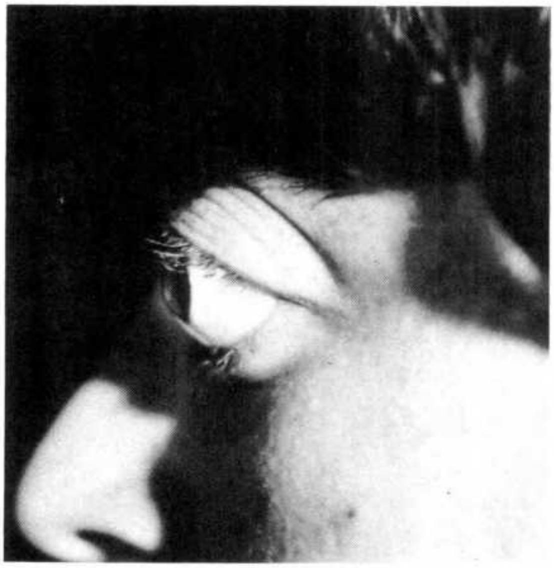

Fig. 2 *LE: Severe exophthalmos in primary position in a patient with craniofacial dysostosis. Appearance of the right eye was the same.*

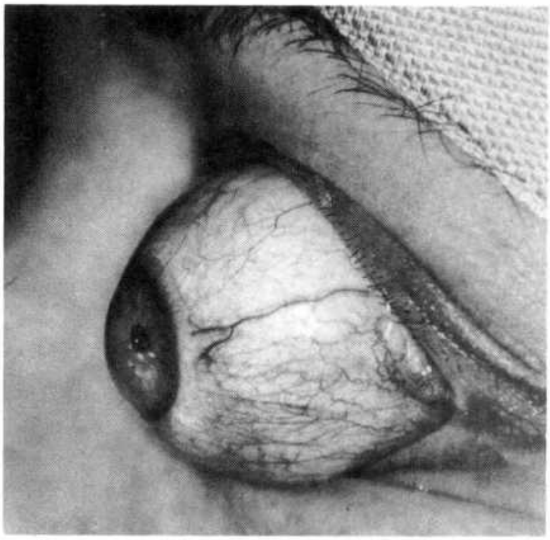

Fig. 3 *LE: Extreme spontaneous luxation of the globe. The right eye was the same.*

eye. Visual acuity was 6/30, −8·0 D, in the right eye and 6/10, −5·0 D, in the left eye. The intraocular pressure (IOP) and anterior compartment were normal in both eyes. In addition exophthalmos (basis 105 mm, right 31 mm, and left 30 mm on exophthalmometry) (Fig. 2), dislocation of the globes (Fig. 3), and myopic retinal degenerative changes were

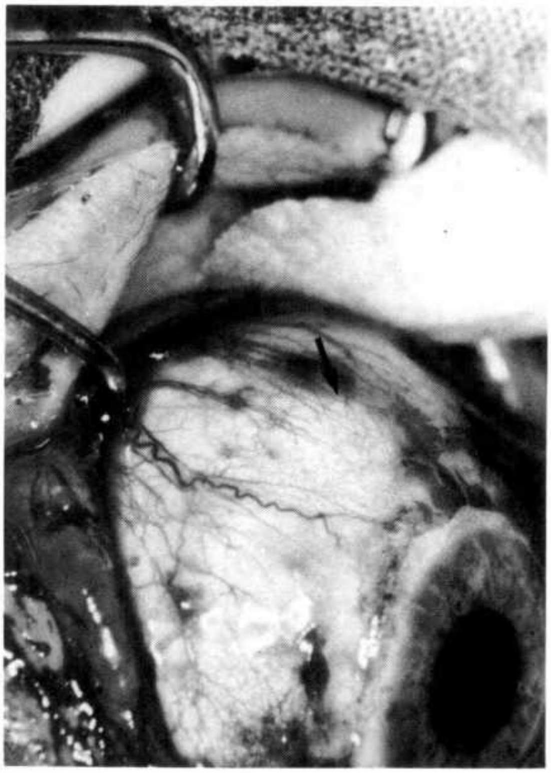

Fig. 4 *RE: A close-up photograph of the eye showing the absence of the superior rectus muscle. The same agenesis of this muscle was found in the left eye.*

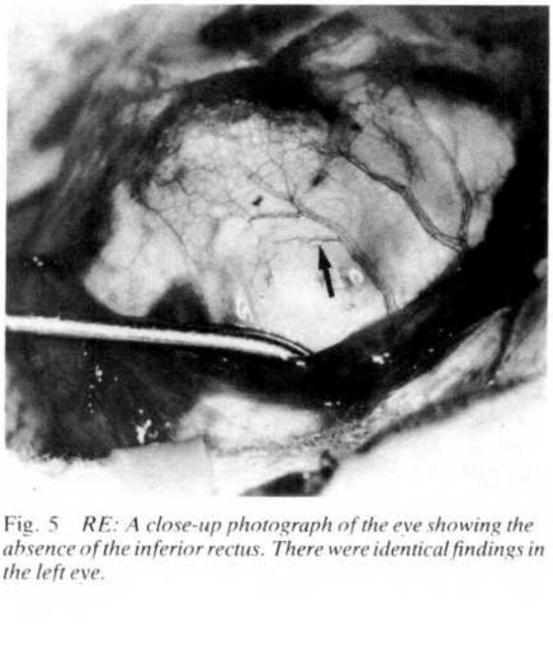

Fig. 5 *RE: A close-up photograph of the eye showing the absence of the inferior rectus. There were identical findings in the left eye.*

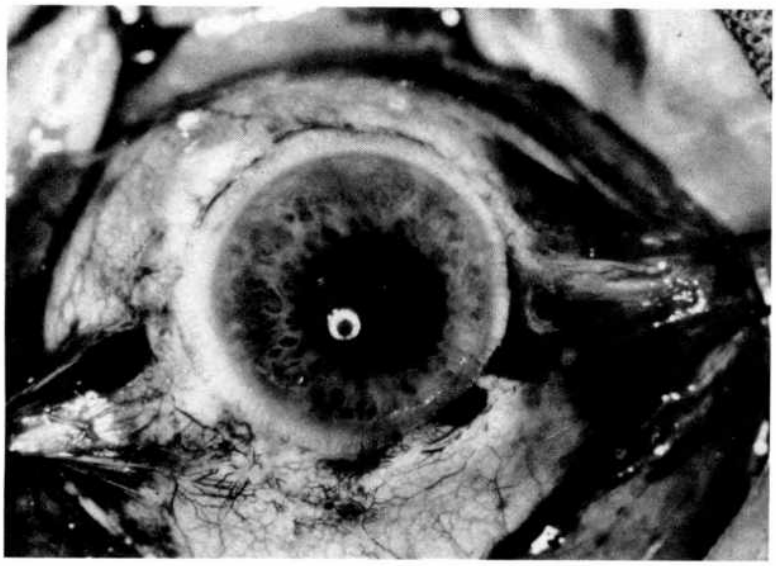

Fig. 6 *RE: The only 2 hypertrophic horizontal extraocular muscles, with wide abnormal insertion anterior to normal locations. Findings in the left eye were identical.*

observed on both sides. The eyes were in divergent position, and, although horizontal gaze was normal, the vertical movements were limited and greatly deficient.

At operation careful exploration of scleral surfaces disclosed the absence of the superior rectus (Fig. 4) and inferior rectus (Fig. 5) and the obliquus muscles. Moreover, there was hypertrophy of the horizontal muscles, with their wide insertion anterior to the normal location (Fig. 6). A continuous band of tissue was also noted extending from the lateral rectus to the medial muscle, which looked like an intermuscular septum.

The patient underwent repair of retinal detachment in the right eye. During the operation, in addition to a 2 mm silicone band (for the correction of the detachment), a special procedure was used in an attempt to retract the eye back into the orbit. The Tenon sheath, which was stretched across the 2 horizontal muscles from above and below, was pulled

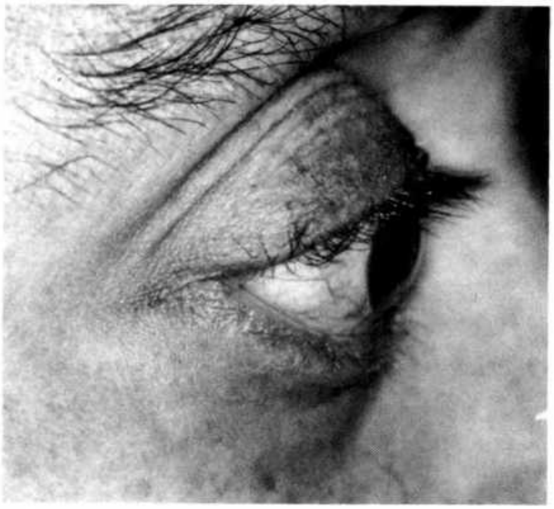

Fig. 7 *RE: A significant reduction of the exophthalmos a few months after the special surgical procedure.*

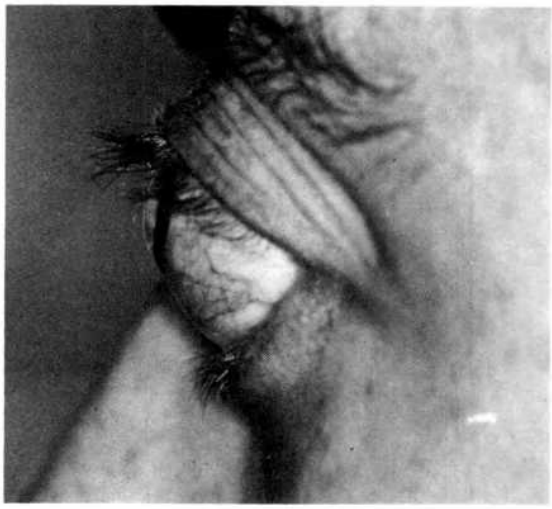

Fig. 8 *LE: A significant reduction of the exophthalmic appearance a few months after the surgical treatment.*

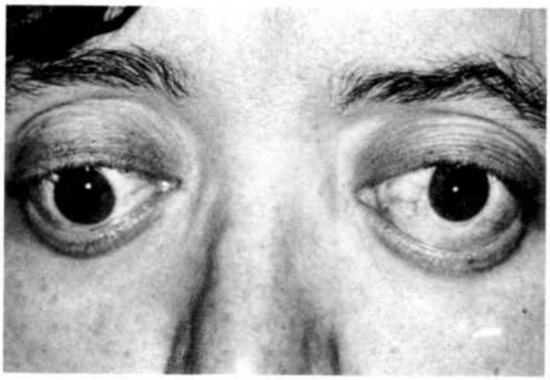

Fig. 9 *Improvement of both eyes, showing retracted positions without luxation 2 years after the operations.*

forward and was then sutured to the sclera about 7 mm from the limbus, with 3 7/0 catgut sutures in each half of the globe. This procedure resulted in an immediate retraction of the globe.

After operation the right eye was considerably more retracted than before the operation, with reduction of the exophthalmos (Fig. 7).

Exophthalmometry measurements were now 26 mm in this eye, without any luxation, and the movements were not essentially improved. However, the patient could close her lids without exposure of the globe. The retinal detachment operation was anatomically successful, with visual acuity 6/30, the same as before the surgical treatment (due to amblyopia).

Since the spontaneous luxation of the left eye disturbed the patient and retraction operation on the right eye had proved successful, the same operation was performed on the left eye 4 weeks later. Scleral exploration revealed essentially the same muscular abnormalities in the left eye; the Tenon sheath in the upper and lower globe was therefore pulled forward and sutured anterior to the equator of the eye. Postoperative examination showed a retraction of 5 mm in the left eye (exophthalmometry measurement was 25 mm, with basis of 105 mm) without luxation (Fig. 8).

After 2 years of follow-up the eyes have remained retracted, with the same exophthalmometry measurements and no dislocation of the globes (Fig. 9).

Discussion

Limitation of eye movement in Crouzon's disease is due both to the shallowness of the orbital cavity and to its position in angulation[2–4,6,8–10,12,13] and to extraocular muscle abnormalities.[1,11,17]

In craniofacial dysostosis there is stenosis of the cranial sutures and shortening of orbital roof by distinctive bulging of the pterion into the temporal fossa, together with increased intracranial pressure of the growing brain on the orbital roof. This pressure phenomenon leads to downward displacement of the floor of the anterior cranial fossa, combined with vertical displacement of the greater wings of the sphenoid bone. Even the orbital floor is reduced as a result of hypoplasia of the maxilla. All these features lead to restricted functional capacity of the orbits which, in turn causes the abnormal position and motility of the eyes.[2–4,6,8–10]

Agenesis of extraocular muscles or abnormal insertion of muscle tendons causes misalignment and defective muscular vectors of action. Two cases of absence of the superior recti were reported by Weinstock and Hardesty.[17] Five cases of absence of superior or inferior recti and obliquus muscles (one muscle in each eye) were described by Diamond *et al.*[11] In addition, Lyle and McGavic (see Walsh and Hoyt[1]) reported on an unusual insertion of the superior obliquus muscle to the eye globe and to the superior rectus muscle.

In the present report the defective position of the eyes, with near total deficiency of vertical and torsional eye motility, was due to the bone malformation and to agenesis of 4 muscles in each eye (the 2 obliquus and vertical recti muscles). The wide insertion of the horizontal muscles in their unusual locations caused the minimal vertical gaze in both eyes.

The reason for the partial underdevelopment of extraocular muscles in such cases is unknown. It may be that an abnormal mutual stimulus between the orbital bones and the extraocular muscles arrests the growth of the ocular muscles.

There are several surgical methods for the prevention of ocular and visual complications. They include complicated procedures, such as orbital decompression by the removal of orbital walls,[13,18–22] midfacial advancement,[18,19,23] and horizontal maxillary osteotomy with advancement and bone graft implantation.[18–23] Each of these surgical procedures has both advantages and disadvantages.[4,12,24]

We used a simple surgical technique—pulling forward the Tenon sheath above and below the eyeball and suturing it to the globe anterior to the equator. By this procedure we improved the cosmetic appearance of the patient, prevented luxation of the eyes, and reduced the exophthalmos.

It is of primary importance to evaluate the presence of all extraocular muscles in Crouzon's disease before beginning complicated neurosurgical and plastic reconstructions. In cases of muscle deficiency in craniofacial dysostosis we suggest this surgical treatment, which will improve the position of the eyes without the harm of other and more complicated procedures.

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British Journal of Ophthalmology, 1982, **66**, 258–263

Ocular motility in alternating squints: an electro-oculographic study

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SUMMARY Ocular movements were studied electro-oculographically in 10 normal subjects and 10 patients with alternating strabismus. Fixation and pursuit movements and to a less extent the saccadic movements were observed to be abnormal in patients with alternating strabismus. The defect in pursuit movements was shown to be statistically significant. There was no correlation between the extent of ocular motor abnormalities and the angle of deviation or the size of facultative suppression scotoma. The possible common pathological mechanism leading to the ocular motor abnormalities qualitatively similar to those reported earlier in strabismus and anisometropic amblyopes are discussed.

Abnormal ocular motility resulting from abnormal sensory adaptations has been demonstrated in amblyopic eyes as well as the fellow eyes of amblyopic subjects. Mackenson[1] reported the existence of unsteady fixation in amblyopes for the first time. Later, saccades[2] and pursuit movements[3–7] were demonstrated in amblyopic subjects, both in the amblyopic eyes as well as the fellow eyes of amblyopic subjects. Mackensen[1] reported the existence of studied. However, no study of ocular motility in other forms of sensory adaptations, such as alternating squint (alternate suppression), has been undertaken. Our intention was to find out if an abnormal sensory experience, in the absence of an obligatory suppression, also leads to abnormalities of ocular motility. This work was therefore undertaken to study ocular motility in subjects with alternating squint.

Material and methods

The study was carried out on 10 normal subjects and 10 subjects with alternating strabismus from the ocular motility and amblyopia clinic of the Dr Rajendra Prasad Centre for Ophthalmic Sciences, New Delhi. A full orthoptic examination was carried out in all subjects. Suppression scotoma was charted by means of foveal fusion slides on the synoptophore.

Ocular motility was recorded electro-oculographically on a multichannel recorder, Mingograph–800. The recordings were carried out at a constant paper speed of 5 mm/s, each small square on the graph paper being 1 mm. Fixation, saccades, and pursuit movements were recorded both in dark- and light-adapted states under standardised conditions for each eye.

Fixation was recorded while the patient looked at a target straight ahead of him. Saccadic movements were recorded as the patient looked from a fixation light on one side to the other, an excursion of 30°. Pursuit movements were recorded with an excursion of 30° to either side.

Analysis of results was carried out by certain modifications of the method described by von Noorden and Mackensen.[4] Grading of fixation, saccades, and pursuit movements was as shown in Figs. 1, 2, and 3. Two other parameters, critical frequency (CF) and frequency of disintegration (FD), were utilised to evaluate the pursuit movements, which allowed the ocular motor abnormalities to be tested statistically.

Results

Critical Frequency (CF). The frequency at which the sine curve first shows a tendency to disintegration was taken as the critical frequency. At this frequency larger jerks were superimposed on the pursuit and the eye slipped from the target for relatively large durations.

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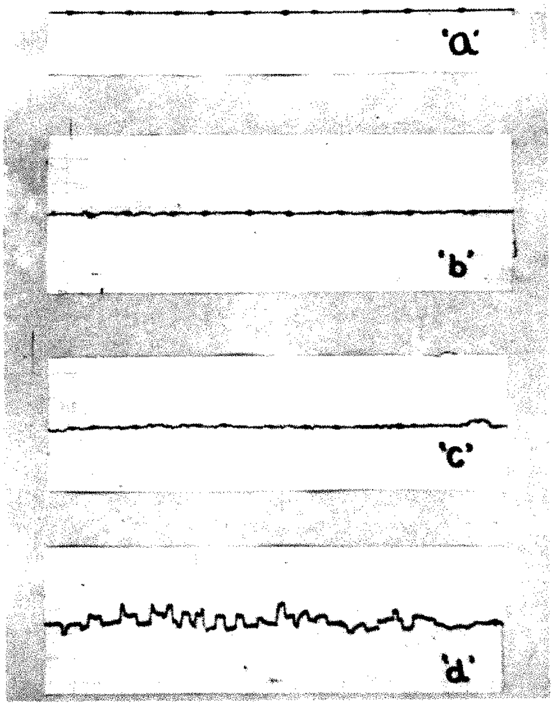

Fig. 1 *Different grades of fixation. (a) Steady fixation. (b) Superimposed small jerks. (c) Pronounced unsteadiness of fixation. (d) Coarse irregular large movements during fixation.*

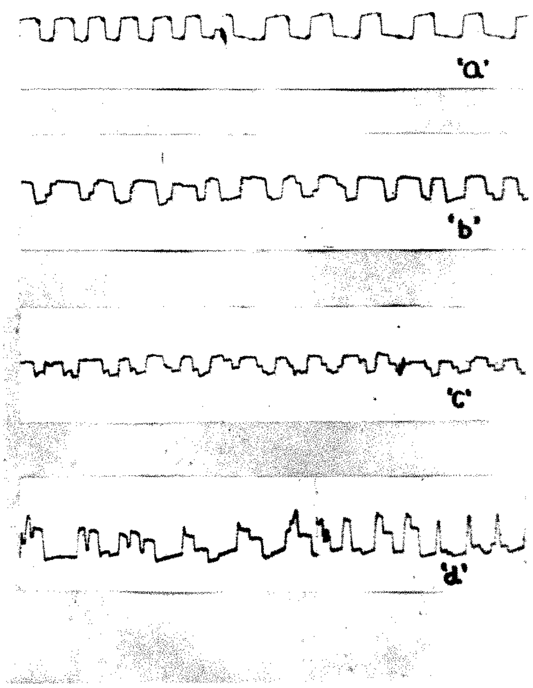

Fig. 2 *Different grades of saccadic movements. (a) Regular smooth saccadic movements. (b) Occasional superimposed jerks in the saccades. (c) Saccades broken into several smaller saccades — mild under- or over-shoots. (d) Saccades almost entirely replaced by jerky deviations, cross-over or undershoots.*

Table 1 *Fixation*

Grade	*Normals*		*Alternators*	
	Dark	*Light*	*Dark*	*Light*
A	8	8	5	4
B	2	1	4	4
C	0	1	1	0
D	0	0	0	2

Table 2 *Saccades*

Grade	*Normals*		*Alternators*	
	Dark	*Light*	*Dark*	*Light*
A	10	9	9	7
B	0	1	1	2
C	0	0	0	1
D	0	0	0	0

Frequency of disintegration (FD). The frequency at which pursuit was totally replaced by saccades and no evidence of pursuit could be seen was termed the frequency of disintegration.

Observations. Abnormalities of ocular motility were often observed in the patients with alternating strabismus. The abnormalities were qualitatively similar to those observed in amblyopic subjects.[7]

Fixation. This was often observed to be unsteady (Figs. 4, 6, 7). Table 1 shows the frequency of abnormalities in fixation in comparison with those in normal subjects. It is apparent that 60% of the alternators had unsteady fixation in the light-adapted state and 50% in the dark-adapted state. Severer grades of abnormality were infrequent.

Saccades. Abnormalities in saccades were infrequent, having been observed in only 30% of subjects in the light- and 10% in the dark-adapted

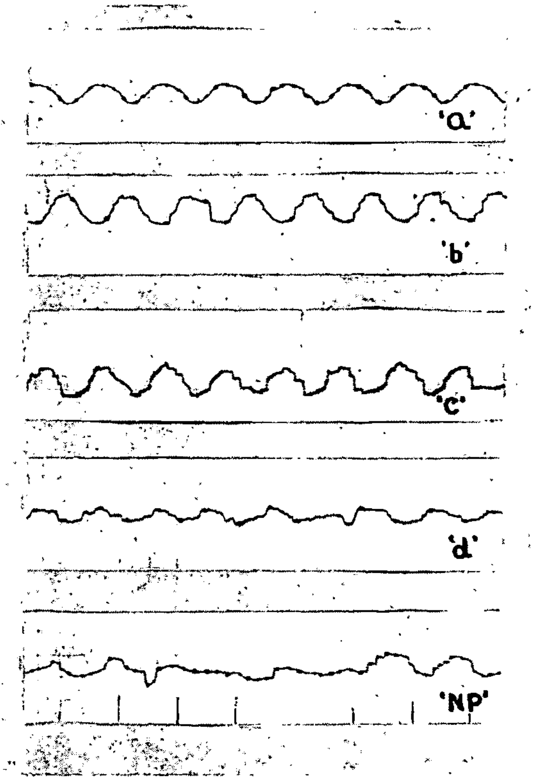

Fig. 3 *Different grades of pursuit movements. (a) Smooth pursuit movements. (b) Superimposed saccadic intrusions on the same shaped curve. (c) Pronounced disturbance of pursuit in form of step ladder pattern. (d) Gross deformation of pursuit movements curve with large intrusions superimposed. (e) NP=No pursuit is evident.*

Table 3 *Pursuit movements*

Grade	*Normals (no. of eyes)*		*Alternators (no. of eyes)*	
	Dark	*Light*	*Dark*	*Light*
A	12	12	5	4
B	5	4	6	7
C	2	3	5	3
D	1	1	3	4
E (NP)	0	0	1	2
Asymmetry	0	0	3	3
Mean CF (cps)	0·62±0·19	0·60±0·19	0·49±0·17	0·44±0·19
p value as compared with normal			0·05	0·02
Mean FD (cps)	0·92±0·19	0·84±0·18	0·70±0·20	0·63±0·21
p value as compared with normal			0·01	0·01

CF=Critical frequency. FD=Frequency of disintegration. NS=Not significant. NP=No pursuit.

state. These abnormalities, as is apparent from Table 2, were usually mild.

Pursuit. Table 3 shows the frequency with which different grades of pursuit were observed in the subjects with alternating strabismus and normal subjects. It is apparent that a much larger number of eyes showed abnormal grades of pursuit than the controls (Figs. 4, 5, 6, 7). No marked difference was apparent between the frequency of abnormalities in the dark- and light-adapted states. The mean critical

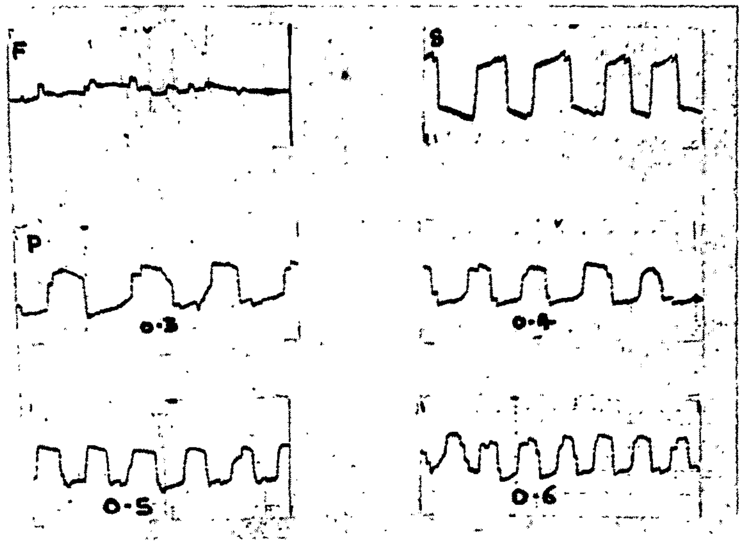

Fig. 4 *Ocular motility in a subject with alternating squint (light-adapted, left eye). Fixation (F): Saccadic intrusions as well as superimposed large saccades. Saccadic (S): Saccadic movements are normal, though fixation at either end is unsteady. Pursuit (P): Pursuit has been totally replaced by saccadic movements; no sine-shaped curve present. (Numerals in pursuit movements indicate speed in cps; paper speed 5 mm/s, each small square 1 mm).*

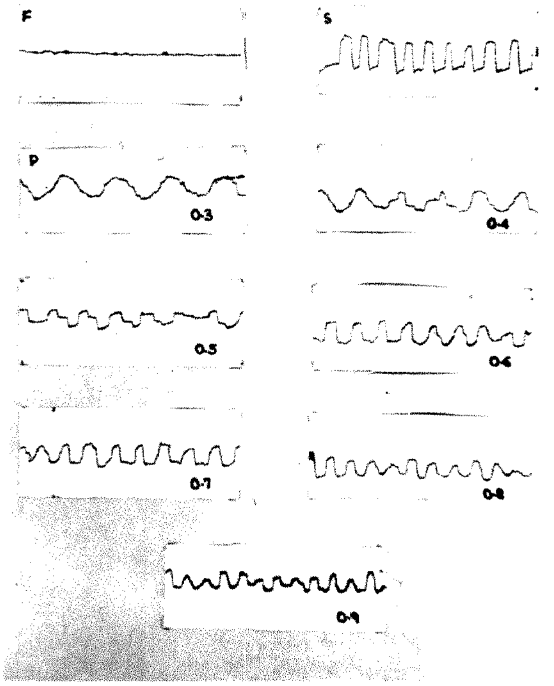

Fig. 5 *Ocular motility in a subject (dark-adapted, left eye). Fixation (F): Saccadic intrusions as well as occasional periods of drifts are present. Saccades (S): Normal. Pursuit (P): Step ladder pursuit at 0·3 cps. Superimposed large saccades on pursuit at 0·4 cps. Asymmetry of pursuit is evident at 0·5, 0·6, 0·7, 0·8 cps). (Numerals in pursuit movements indicate speed in cps. Paper speed 5 mm/s, each small square 1 mm).*

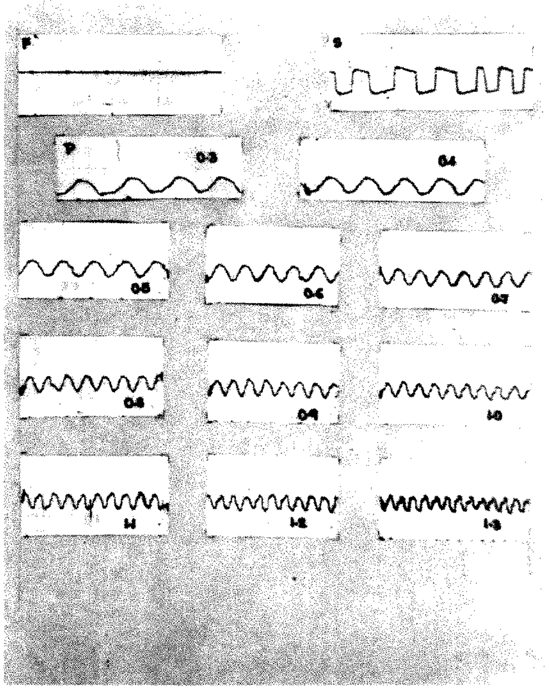

Fig. 6 *Ocular motility in another subject with alternating squint (dark-adapted, left eye). Fixation (F): Normal, steady fixation. Saccades (S): Normal. Pursuit (P): Smooth pursuit at lower speeds, except for occasional saccadic intrusions. Obvious asymmetry of pursuit at higher speeds (0·9, 1·0, 1·1 cps). (Numerals in pursuit movements indicate speed in cps. Paper speed 5 mm/s, each small square 1 mm).*

frequency (CF) in the alternators in the dark-adapted state was 0·49±0·17 counts per second (cps) as compared with 0·62±0·19 cps in normal subjects and 0·44±0·19 cps in comparison with 0·60±0·19 cps in control subjects in the light-adapted state. The values were significantly lower in the alternators ($0{\cdot}05 > p > 0{\cdot}02$ in dark- and light-adapted states respectively).

The mean frequency of disintegration (FD) in the alternators in the dark-adapted state was 0·70±0·20 cps (normal subjects 0·92±0·19 cps) and 0·63±0·21 cps (normal subjects 0·84±0·18 cps). The values were significantly lower in alternators ($p < 0{\cdot}01$) in both dark- and light-adapted states. The values of CF and FD in dark- and light-adapted states were not significantly different from each other.

Asymmetry of pursuit in nasal and temporal movement (Figs. 5, 6) was observed in 3 eyes of 2 subjects. This asymmetry could not be related to the existence of asymmetry of facultative suppression scotoma in these subjects.

Correlation of different parameters with ocular motor abnormalities. No correlation was found between the extent of ocular motor abnormalities and either angle of deviation or size of facultative suppression scotoma.

Discussion

This study shows that ocular motor abnormalities like those observed in amblyopic subjects exist in patients with alternating squint as well. Thus even in alternators, in whom obligatory suppression is absent, some common factor may operate in the causation of ocular motor abnormalities like those in strabismic and anisometropic amblyopes. This factor

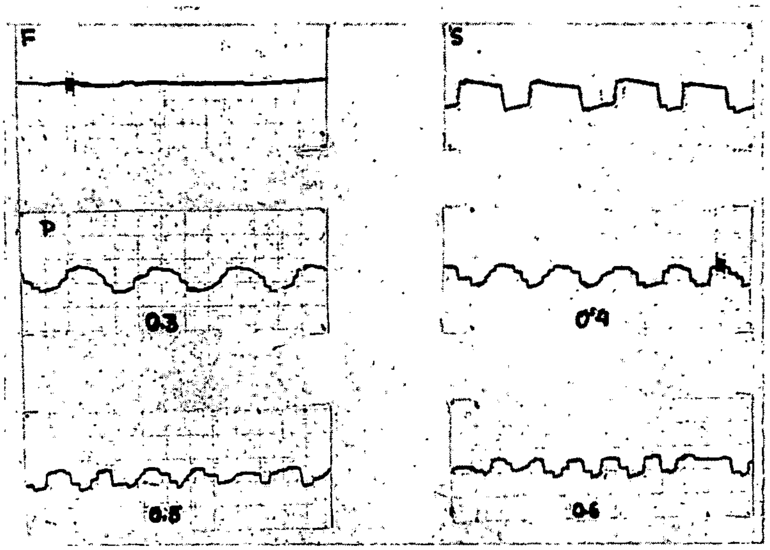

Fig. 7 *Ocular motility in another subject with alternating squint (dark-adapted, right eye). Fixation (F): Periods of drift are present. Saccades (S): Normal. Pursuit (P): Step ladder pattern (cog wheeling) of pursuit at low speeds. Early disintegration of pursuit. (Numerals in pursuit movements indicate speed in cps. Paper speed 5 mm/s, each small square 1 mm).*

could be an abnormal sensory experience during the 'critical period.' The exact mechanism by which the primary sensory anomaly leads to ocular motor abnormalities is not clear. The results suggest that the ocular motor abnormalities may result from abnormalities in the binocularly driven cells of the occipital cortex, which in turn may result from an abnormal sensory input during the critical period. These binocularly driven cells are the source of afferent stimuli to the occipital and probably the frontal oculomotor system. That an abnormal input to the occipital oculomotor system could affect the 'position maintenance system' and the 'pursuit system' is quite possible. The observations made in the present study showed the defect in fixation and pursuit movements to be much more frequent while the defect in saccadic movements was markedly less frequent, suggesting that the occipital oculomotor system is affected to a greater extent than the frontal oculomotor system.

A number of workers have demonstrated an alteration in the dominance of eyes and a decrease in the number of binocularly driven cells of the striate cortex by abnormal sensory stimulation in the critical period. Such observations have been made on young kittens by monocular occlusion[8,9] and by producing artificial strabismus[10] or by alternate occlusion.[10] Similar results have been demonstrated in monkeys by stimulus deprivation[11] and by induced strabismus.[12] Thus it is conceivable that an abnormal sensory experience in the critical period, such as strabismus, anisometropia, or alternating strabismus may affect the binocular cells of the occipital cortex.

This study is therefore in agreement with that of Fukai *et al.*,[13] who postulated an abnormality in the binocular cells of the occipital cortex as responsible for abnormal ocular motility in the amblyopes. The study of ocular motility in subjects with alternating squint lends further support to this pathological mechanism.

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British Journal of Ophthalmology, 1982, **66**, 264–268

'Preferential looking' for monocular and binocular acuity testing of infants

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SUMMARY A method is described for obtaining rapid and reliable estimates of acuity in infants, for both monocular and binocular viewing. The method depends on 'preferential looking', where the infant prefers to look at a striped pattern rather than a blank screen of matched mean luminance. A staircase procedure for testing is followed, with observations being recorded by a 'blind' observer (who does not know on which of the 2 screens the striped pattern is displayed). Monocular acuity estimates have been obtained for a group of infants 3 to 4 months old with normal refractions. Many of these infants show similar acuity values in the 2 eyes, with a few showing reliable differences between the eyes. To check reliability of the method a comparison of 2 independent interleaved staircase estimates of the same eye have been made. In general this check shows highly consistent estimates for a given eye of a given infant. Nearly all infants show slightly higher acuity estimates for binocular viewing than for monocular. The possible reasons for this difference are discussed. The clinical use of such a method is reported for a number of cases. The method has been found to be useful in a variety of clinical conditions where other available tests are not possible on young infants.

The forced-choice preferential looking (FPL) method is now well established as a means of estimating acuity and other visual detection performance in infants aged 1–6 months.[1–5] The present authors have been using it routinely to assess clinical acuity deficits in this age range, as have others. Published work has generally used FPL with a binocularly viewing infant. However, clinical assessment is usually required for each eye separately. In many instances it is the possible difference between the eyes which is the major concern. Binocular relationships have also been the principal focus of recent work in the developmental neurobiology of vision,[6 7] and therefore measurements of the performance of each eye separately are required if research on normal and abnormal visual development in infancy is to be related to these studies.

The study reported here was therefore intended to test whether reliable determination of monocular acuity was possible by FPL, what variation of acuity between the eyes would be found in a presumptively normal group of infants using this technique, and whether the method would permit the detection of clinically significant interocular differences. As well as these trials of the method on normal infants we describe our experience in the practical use of the method for monocular and binocular testing of infants referred for acuity testing for a variety of clinical reasons.

Material and methods

The apparatus and general procedure resembled that described by Atkinson *et al.*[3] Infants were seated on a holder's knee 57 cm from a pair of oscilloscope screens, at which distance the diameter of each screen subtended 10·5° and the separation of the screens 6·3°. Between trials both screens displayed a uniform field of luminance 30 cd/m^2, and a set of lights midway between the screens attracted the infant's attention. A concealed observer watched the infant from a central peephole above the screens, and initiated a trial when the infant was fixating centrally. During the trial one of the screens (selected automatically at random) was modulated by a high-contrast horizontal sinusoidal grating while the other remained uniform and of equal mean luminance. (The gratings moved

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steadily with a temporal modulation rate of 3 Hz.) The observer was unaware of which side the grating was displayed and had to make a forced choice of this based on observation of the infant's fixations and other behaviour. The duration of the observation period necessary for this was under the observer's control up to maximum of 10 seconds and was typically 5 seconds or less for infants of the age tested in this study. If on any trial an infant was not looking at either screen the observer could abandon that trial without having to make a forced-choice judgment.

For monocular testing an adhesive orthoptic patch was placed over the left or right eye. The observer checked the alertness and lack of fussiness of the infant by presenting a low spatial frequency grating (0·5 c/deg), and checking that the infant made a clear observable eye movement to the display on the side of the pattern. The infant's position in front of the screens was arranged so that before the pattern was presented the viewing eye was in line with the central fixation lights.

A series of spatial frequencies (grating stripe widths) were chosen in which each frequency was higher than the one below by a factor of 1·6 (two-thirds octave). Testing was started with 5 trials using a grating of 2 c/deg. After this the spatial frequency used for each block of 5 trials was selected according to a 'staircase' rule.[8] That is, if on the previous block the observer had made 4 or 5 correct choices the spatial frequency was increased by one step for the next block. Two or fewer correct choices led to the next lowest spatial frequency being used in the next block. If there were 3 correct choices out of 5, the frequency remained unchanged; if this occurred on 3 successive blocks, the next frequency was chosen in the direction most likely to meet the criterion for completing the staircase.

A staircase was taken as complete when at least 20 trials had been run at each of 2 adjacent frequencies, with the proportion of correct responses bracketing or including the value of 70%. Normally between 50 and 90 trials were needed to meet this criterion. The acuity value was taken as the 70% point obtained by interpolation between these 2 spatial frequencies.

To test acuity of the 2 eyes under conditions which were as comparable as possible in terms of the infant's state we used a method of 'interleaved staircases.' Twenty-five trials (i.e., 5 blocks) were run with one eye occluded; the occluding patch was then switched to the other eye and a new staircase sequence was followed for 25 trials.

The patch was then put back on the first eye, the next block of 25 trials followed the original staircase from where it had been left off, and so on. An example of the procedure is illustrated in Fig. 1. To assess the reproducibility of measurements made with our technique we tested some other infants with the same procedure of 2 interleaved staircases but with both independent staircase sequences testing the same eye. We shall refer to this as 'series 1/series 2 comparison.'

The infants volunteered by their parents to help in this study were from the Cambridge area. All infants had normal birth histories and were not more than 10 days premature. The mean age of testing on the first visit was 16 weeks (3½ months). Testing on each

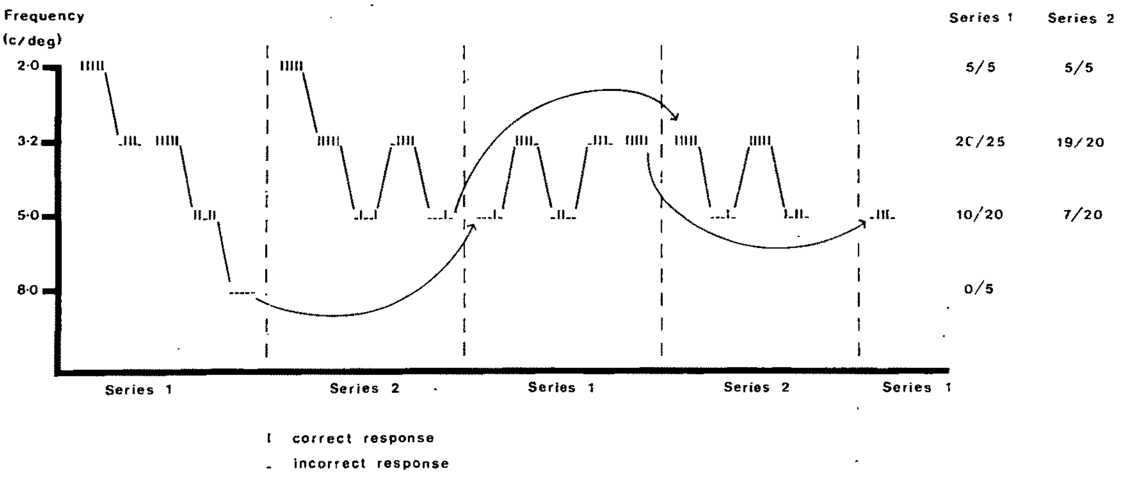

Fig. 1 *An example of the procedure used for infants who were tested with 2 independent staircases on one eye to obtain 2 interleaved estimates of acuity.*

child was completed within a period of 14 days. To complete the testing most infants made 3 visits; a few completed testing in 2 visits and a few took up to 5 visits. They were tested when alert and calm, usually after a feed. No testing period was longer than 15 minutes.

All the infants were photorefracted under conditions of free accommodation[9] to detect any refractive errors which might affect the comparisons being made. No infant showed any difference between the eyes greater than 0·5 D in any meridian.

Twenty-nine infants were tested in all, of whom 4 did not complete monocular testing because of fussiness and so are not included in the results. The remaining 25 received different conditions of testing in various sequences, outlined in the results section.

Results

Sixteen infants received interleaved staircases viewing with the left and right eyes. The acuity values obtained are indicated by solid circles on Fig. 2. This figure also includes data from 7 infants for whom each eye was tested but not in interleaved staircases, because they were initially in the group for series 1/series 2 comparison (open circles on Fig. 2). In most cases measurements on the 2 eyes showed good agreement (i.e., the points lay close to the 45° line). The median ratio of measured acuity between the eyes (ratios always taken as greater than 1·0) was 1·12. However, a few individuals showed a more marked interocular difference, which was as large as 2·0 in 2 cases.

To estimate the reliability of these figures we have the comparisons of series 1/series 2 shown in Fig. 3. These data are from 6 infants for whom series 1/series 2 were interleaved for one eye, and from each eye of 3 further infants for whom series 1/series 2 were obtained on both eyes. (Data from the latter infants are included in Fig. 2 also.) All data points lay very close to the 45° line (median acuity ratio for the two series=1·06; maximum ratio=1·20). It appears therefore that the variations seen in Fig. 2 are not a consequence of variability in the method but reflect the range of genuine interocular differences at this age.

Fig. 4 shows the results of comparing binocular and monocular acuity determinations on the same infants. The monocular acuity shown was the better of the 2 values for each infant except in the 2 cases represented by open circles, in which only one eye received monocular testing. None of the binocular testing was interleaved with monocular testing. In general the estimated binocular acuities were higher than the better monocular acuities. There are several possible reasons for this difference between

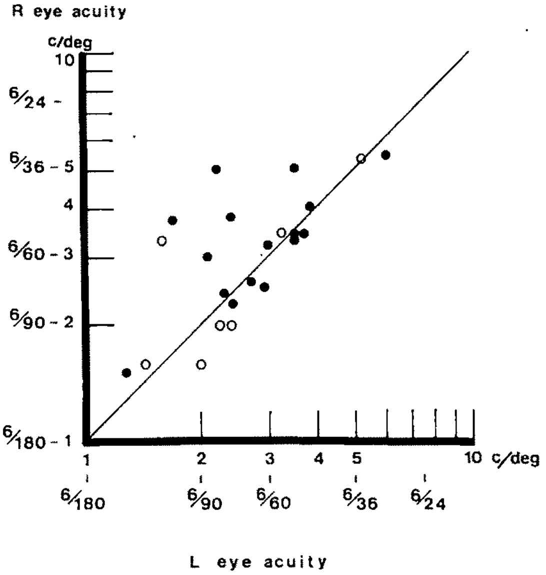

Fig. 2 *Acuity estimated for R and L eyes of 23 infants. The filled circles are infants where the 2 eyes' estimates were interleaved, the open circles are for noninterleaved results. Outer scales give Snellen equivalent of the acuity measures.*

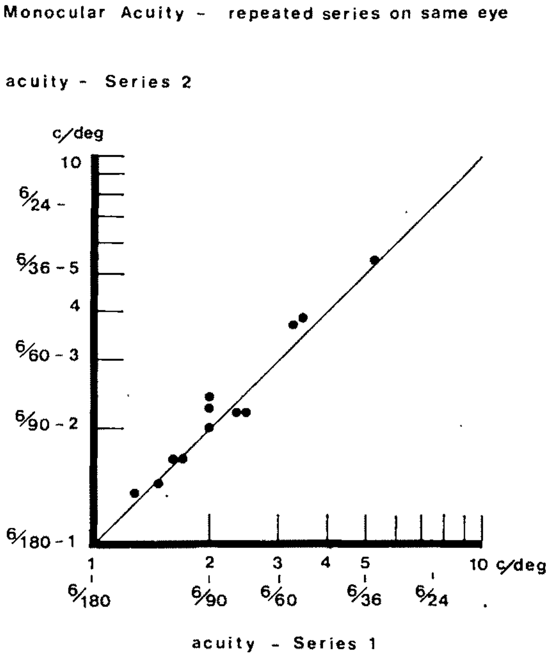

Fig. 3 *Comparison of 2 acuity estimates with the same eye for 12 eyes from individual infants. The 2 estimates were interleaved in blocks of 25 trials.*

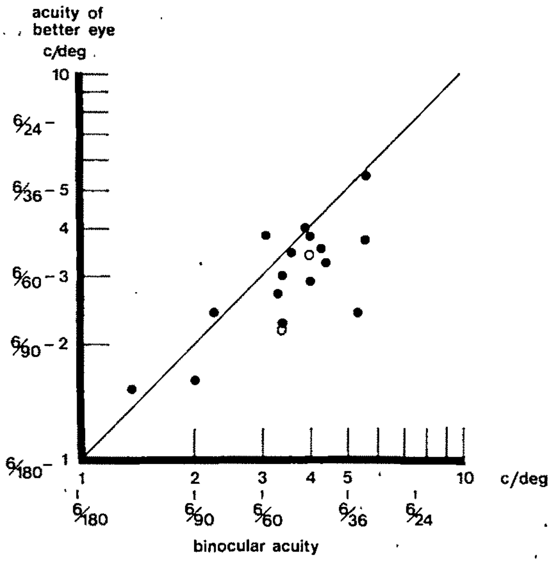

Fig. 4 *Comparison of estimates of binocular acuity with the highest monocular acuity for 16 infants. The 2 open circles are for 2 infants for whom only one eye's acuity was estimated.*

monocular and binocular results. It may be that infants' binocular resolution is genuinely better than monocular, as has been reported for adults. However, we do not believe that the data give strong evidence for such a sensory effect, since the infants were in an overall calmer state when they were not wearing a patch. While we made every attempt to conduct monocular and binocular testing with the infants in similar state and over a similar time, testing was usually more difficult when a patch was used. Further, as the binocular testing was on a later session than monocular, there may have been some binocular advantage from the rapid development of acuity at this age. This would be overcome by interleaved monocular and binocular testing.

CLINICAL USE OF THE METHOD

A number of clinical cases have been successfully tested by using the procedure. It is hoped that some of these infants will be followed up by different tests when they are older.

In general the procedure has proved useful in assessing vision in 3 groups.

(1) Infants in whom there is a suspected problem in one eye. Infants in this group were tested monocularly as in the study reported above. The age of the infant appears to be the critical factor determining the possible length of testing. Infants older than 9 months were difficult to test monocularly and in general did not attend long enough to complete the staircase procedure. So far 41 infants have had monocular assessments of acuity. Ten of those had congenital convergent strabisimus, 7 of whom were tested before and after surgery. The other cases in this group were infants with high refractive errors (anisometropia, large oblique astigmatism requiring monocular testing with different grating orientations for the 2 eyes), corneal opacities or scarring, intermittent divergent strabismus, congenital cataract, nystagmus, coloboma, ptosis, microphthalmia, ophthalmia neonatorum. Many of the cases have had multiple assessments at different ages in the first year of life. A typical case is of a baby who was 8 weeks premature, with respiratory problems at birth, and intermittent left convergent strabismus. Tested at 6 months the LE acuity was 1·2 c/deg (6/150), RE acuity 2·5 c/deg (6/72).

Monocular assessments according to the procedure described were completed on 17 of these infants under 9 months of age and on 5 aged between 9 and 18 months. In 14 (all over 9 months) acuity estimates had to be derived from incomplete staircases, and in 5 cases the infants were not sufficiently co-operative for any useful testing.

(2) Infants with suspected poor sight, partial vision, or blindness. In general, if testing is binocular, a reliable assessment of acuity can be obtained for infants slightly older than when monocular assessment is required. The types of clinical disorders included in this group are large refractive errors, coloboma, hydrocephalus, cortical blindness, congenital nystagmus, microphthalmia, strabismus, birth trauma, and encephalitis. Out of 58 infants tested 14 under 9 months of age completed testing; 41 over 9 months of age had acuities estimated from abbreviated staircases (20–25 trials rather than 40–100 trials), and 3 infants over 9 months of age were uncooperative.

A typical case in this group was a baby with coloboma of iris, lens, and choroid, tested at 2·5 months old, binocular acuity 1·0 c/deg (6/180); 5 months, 3·0 c/deg (6/60); 8 months, 3·0 c/deg (6/60).

(3) Children with developmental delay suspected of partial sight or blindness. In general these children are passive and easy to test because the response required from the child is minimal. To date 10 children in this category have been successfully tested; 6 of these children have delay of unknown aetiology, one child had severe tuberculous meningitis, one viral encephalitis, one intracranial haemorrhage at birth leading to hydrocephalus, and one agenesis of the corpus callosum.

An example of such a case was a baby aged 2·5 years with severe mental retardation (mental age approximately 4 months) and binocular visual acuity 4 c/deg (6/45).

Discussion

The results of Figs. 2 and 3 show that reliable monocular estimates of acuity are possible with infants by the preferential looking (PL) method, although it demands more attention to infant handling than binocular use of the same method. PL is, therefore suitable for clinical assessment of monocular as well as binocular disorders of infant vision. But we have also shown measurable differences in interocular acuity in presumptively normal 3-month-olds. The reason for these differences is not known. However, it is perhaps not surprising that in a period of rapid acuity development[10] the 2 eyes might sometimes be found to be at slightly different stages of that development. We presume that such differences are transient. Acuity differences of a factor of more than 2, or differences that persist, may be considered as probable indications of abnormality.

In the PL procedure to assess acuity in clinical cases we find it more successful in infants under 9 months (or equivalent developmental age) than in older infants. Estimates are often possible for the older infants, but it is frequently not possible to maintain the infant's attention long enough to complete the staircase procedure described here. We hope that it may prove possible to apply more sophisticated statistical procedures to PL testing[11 12] and thereby reduce the number of trials necessary to achieve a reliable threshold estimate.

There is still a great need for a robust test suitable for children over 9 months but too young for subjective tests such as the Sheridan-Gardiner. The tracking tests such as Catford drum[13] and Stycar balls[14] suffer from some shortcomings in target design and procedure.[15] We are currently exploring the application of tests which depend on tracking but use stimuli that are genuine resolution targets, and which maintain the principles of forced choice by a blind observer and staircase determination of threshold which we have applied in the PL test.

This work was supported by the Medical Research Council. We would like to thank our clinical colleagues from the Department of Ophthalmology (especially Mr P. G. Watson and Mr J. Keast-Butler) and the Department of Paediatrics, Addenbrooke's Hospital, Cambridge, for referring their infants to us and for helpful discussions of the results.

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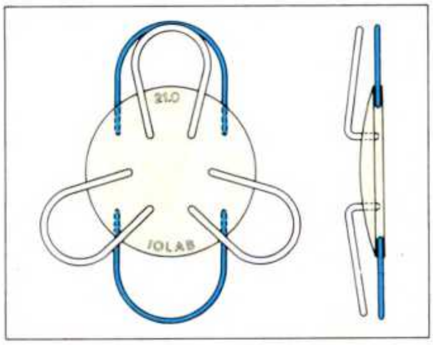

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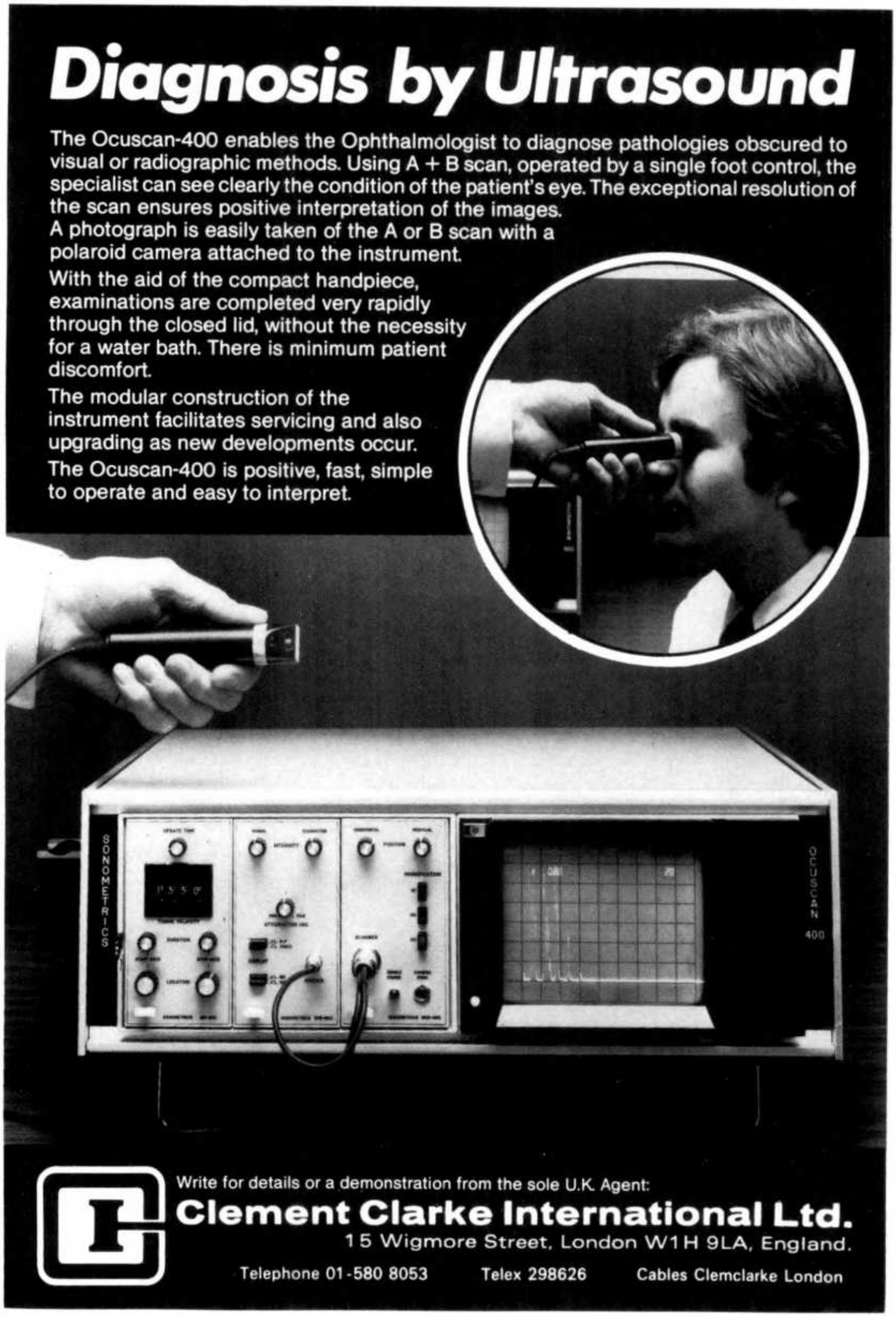

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Computed tomography in the management of orbital infections associated with dental disease

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SUMMARY Two patients developed orbital infection secondary to dental infections. In one patient the infection spread from maxillary premolar and molar teeth to the infratemporal and pterygopalatine fossa and then through the inferior orbital fissure to the subperiosteal space. A subperiosteal abscess in the posterior lateral orbital wall developed, which subsequently spread within the muscle cone. In the second patient infection of an anterior maxillary tooth caused a pansinusitis and unilateral orbital cellulitis. In both patients computed tomographic scanning of the orbit proved valuable in localising the infection and, in one case, planning a surgical approach to the orbit. The infection in both patients responded to treatment, with no permanent visual impairment. Appropriate antibiotics and prompt identification and surgical drainage of orbital abscesses are essential for the preservation of vision in cases of orbital infection.

Although dental infection has been recognised as a source of orbital cellulitis since the time of Hippocrates,[1] attention to this association in the recent ophthalmic literature has been sparse. In the preantibiotic era orbital cellulitis was commonly associated with dental abscesses and maxillary sinus involvement. The widespread use of prophylactic and therapeutic antibiotics has decreased the incidence of ocular complications of odontogenic infections, although occasional cases still occur.[2–5] Orbital cellulitis can often be managed medically; however, surgical drainage is usually necessary if a localised abscess develops in the orbit.[6 7] Computed tomography has aided in the evaluation and management of orbital lesions,[8 9] including orbital cellulitis.[10 11] We describe 2 cases of orbital infections associated with dental disease in which computed tomographic scanning proved useful in patient management.

Case reports

CASE 1

A 30-year-old man had a 4-day history of swelling of his left upper cheek. With the patient under local anaesthesia incision and drainage of an abscess in the left buccal space were performed. The carious teeth were not removed. He was treated with oral penicillin. The patient returned 2 days later with increased pain and swelling of the left cheek. 30 ml of purulent material was drained from the same abscess. The following day the patient had signs of infratemporal space extension of the infection. He was admitted into the hospital and started on a regimen of 2 million units of intravenous penicillin G every 4 hours. Approximately 3 hours after admission the patient became somnolent; his temperature was 40·5°C (105°F). Decreased abduction of the left eye was noted. The dose of intravenous penicillin was increased to 5 million units every 6 hours, and intravenous nafcillin sodium, 2 g every 6 hours, was added. The morning after admission an ophthalmological consultation was requested.

Ocular examination showed that visual acuity was 6/6 (20/20) without correction bilaterally. The pupils were equal and reactive to light. There was no afferent pupillary defect. 6 mm of left proptosis was present. Diplopia was noted in all fields of gaze except the primary position. Ductions of the right eye were full. In the left eye there was an 80% reduction in abduction and a 50% reduction in adduction,

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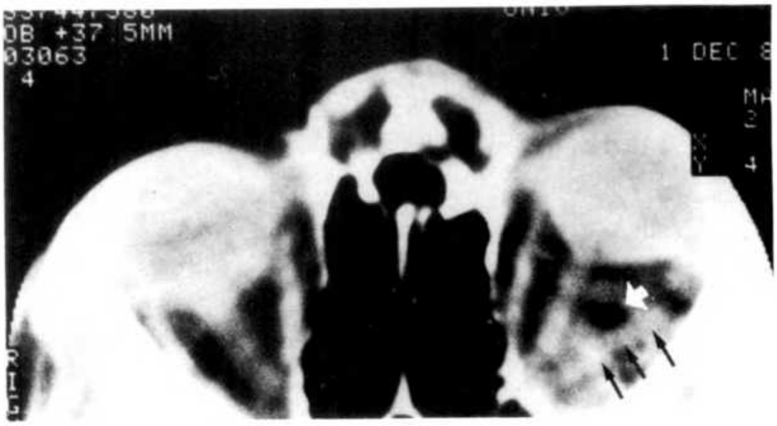

Fig. 1 *Case 1. Computed tomographic scan of the orbits without contrast medium shows medial displacement of the left lateral rectus muscle (black arrows) by a subperiosteal abscess at the apex of the orbit that extended along the lateral orbital wall. An intraconal abscess with gas (white arrow) and significant left proptosis also are shown.*

elevation, and depression. Minimal left inferior conjunctival chemosis was present, but the slit-lamp examination was otherwise unremarkable. Applanation tonometry was normal bilaterally. The findings on dilated ophthalmoscopic examination were within normal limits. Skull and sinus *x*-ray films revealed a soft-tissue density in the left maxillary sinus. The ethmoidal sinuses were clear.

On the day after admission the patient was given general anaesthesia, and the carious left maxillary, first and second premolars, and first, second, and third molars were removed. Incision and drainage of the left infratemporal space were performed. A left Caldwell-Luc procedure and nasal antrostomy were performed. The maxillary sinus was noted to be clear. Purulent material was drained from the left buccal and infratemporal spaces, and drains were placed at both sites. Through an external approach a sterile swab was inserted into the pterygopalatine space, and material for cultures was taken. These cultures subsequently grew streptococci and *Bacteroides melaninogenicus* (subspecies *intermedius*). Postoperatively intravenous gentamicin, 80 mg every 8 hours, was added to the preoperative antibiotic regimen of penicillin and nafcillin.

During the next 2 days chemosis and proptosis increased. The patient's left ocular motility was reduced by 90% in all fields of gaze. His temperature intermittently spiked to 39·4°C (103°F). The infratemporal incision continued to drain purulent material. Visual acuity remained unaffected until the fifth day in hospital, when it was noted to decrease to 6/15 (20/50) in the left eye. At this time 8 mm of left proptosis was present. The ophthalmoscopic examination of the left eye showed disc hyperaemia and oedema, with a single retinal haemorrhage. A cotton-wool spot was present along the inferotemporal arcade. Goldmann visual field testing showed a central scotoma in the left eye. Computed tomographic scan disclosed a left subperiosteal abscess at the apex of the orbit that extended along the lateral orbital wall and a secondary intraconal abscess with gas (Fig. 1). The intraconal abscess was enhanced with the use of intravenous iodinated contrast medium (Fig. 2).

With the patient under general anaesthesia a left subperiosteal approach along the inferolateral orbital wall was made to drain 3 ml of purulent material from the subperiosteal abscess 25 mm from the orbital rim. The maxillary sinus was explored, and a blood clot was removed from the antrum. There was no evidence of infection in the maxillary sinus. The orbit was then decompressed into the maxillary and ethmoidal sinuses by removing portions of the floor and medial wall of the orbit. A lumbar puncture at the completion of the procedure yielded normal findings. Cultures from the subperiosteal abscess grew *Bacteroides melaninogenicus* (subspecies *intermedius*), the same organism previously cultured from the infratemporal fossa and the pterygopalatine fossa. Postoperatively defervescence was achieved with an antibiotic regimen of penicillin, nafcillin, and gentamicin. During the next 2 weeks visual acuity returned to 6/6 (20/20) and visual fields returned to normal. The proptosis also resolved, and the patient had only slight restriction of abduction of the left eye.

CASE 2

A 20-year-old black woman noted pain in the area of her right second maxillary bicuspid tooth 2 days after she lost a dental filling from that tooth. The carious right second maxillary bicuspid was promptly removed by her dentist. The following day she had slight swelling on the right side of her face and pain on moving her right eye. Two days after the tooth extraction she returned to her dentist, and he prescribed oral penicillin for her. The following

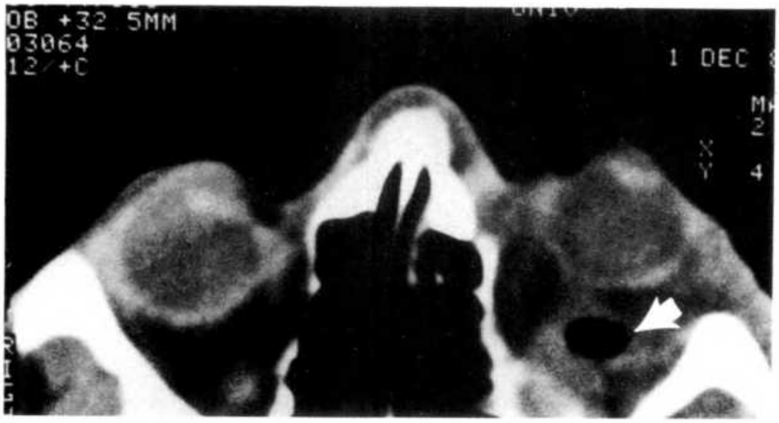

Fig. 2 *Case 1. Computed tomographic scan with the addition of iodinated contrast material enhances the appearance of gas within the intraconal abscess (white arrow). The scan is at a slightly different level than Fig. 1.*

morning she noted swelling of the right eyelid, protrusion of her right eye, and diplopia on vertical gaze. She sought ophthalmic consultation and was admitted to the hospital.

Her past medical history was positive for haemoglobin SC disease with proliferative sickle cell retinopathy in the right eye. Three years previously she had undergone argon laser photocoagulation. The patient also had a long history of asthma for which she was taking bronchodilators, including terbutaline sulphate and theophylline. The patient denied having had any previous sinus problems.

On physical examination the patient was alert and had a temperature of 37·8°C (100·2°F). The right side of her face was swollen. On opening her mouth she experienced right-sided temporomandibular joint pain with slight trismus. A few cervical and preauricular lymph nodes were palpable on the right side. There was no pain on palpation of her frontal or maxillary sinuses. Intraoral examination showed normal healing of the extraction site. There was no palatal or vestibular swelling, although the vestibule was tender to palpation. No evidence of an oral-antral communication was observed.

Ocular examination disclosed a visual acuity of 6/6 (20/20) in both eyes. Her pupils were equal and reactive to light without an afferent pupillary defect. Duction testing of the right eye showed reduction of abduction and adduction by 20% and reduction of up and down gazes by 50%. Diplopia was present on vertical gaze. She had 6 mm of right proptosis. External examination demonstrated moderate swelling and erythema of the right eyelids. The conjunctiva was normal. Slit-lamp biomicroscopy and applanation tonometry examinations were unremarkable. A normal disc and macula were noted on ophthalmoscopic examination of the right eye. In the temporal periphery an elevated, fibrous, nonperfused sea fan was visible. Argon laser photocoagulation scars were evident. The fundus of the left eye showed evidence of nonproliferative sickle cell retinopathy, with a few scattered sunbursts and iridescent spots.

The patient's haematocrit level was 40%. The white blood cell count was $22{\cdot}4\times10^9/l$, with 94% polymorphonuclear leucocytes, 2% band cells, 3% lymphocytes, and 1% monocytes. Sinus *x*-ray films demonstrated bilateral opacification of the frontal, sphenoidal, and ethmoidal sinuses. The left maxillary sinus showed mucosal thickening. There was an air fluid level in the right maxillary sinus. Periapical dental *x*-ray films of the extraction site showed no evidence of tooth fragments; however, the apex of the extraction site was in close proximity to the maxillary sinus. Blood and nasal discharge cultures showed no growth. The patient was treated with intravenous ampicillin, 1 g every 6 hours, and intravenous oxacillin, 1 g every 4 hours. She was also put on a regimen of nasal decongestants, postural drainage, and warm compresses to the face. The day after admission she showed no improvement. A computed tomographic scan of the orbits was obtained. It showed soft-tissue swelling posterior to the orbital septum in the area of the right medial rectus muscle without definite evidence of abscess formation (Fig. 3). On the third day the patient's fever abated and she noted marked relief in pain. Objectively there was some improvement in ocular motility. After 5 days of parenteral antibiotics the patient's ocular motility returned to normal. Lid swelling and proptosis were decreased. Repeat sinus *x*-ray films revealed resolution of the air fluid level of the right maxillary sinus. The parenteral antibiotics were discontinued, and the patient was treated with oral oxacillin, 500 mg 4 times a day. On follow-up examination one week after discharge ocular motility was normal and there was complete resolution of proptosis.

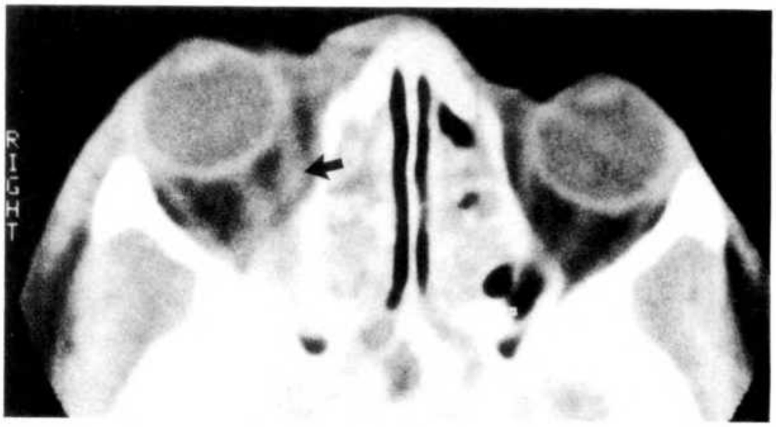

Fig. 3 *Case 2. Computed tomographic scan of the orbits without contrast medium shows soft tissue swelling within the right orbit in the region of the right medial rectus muscle (arrow). Both ethmoidal sinuses are opacified, and right proptosis is shown.*

Discussion

Although the use of antibiotics has decreased the incidence of orbital complications of odontogenic infection, dental disease may still cause infections,[6 12] including preseptal cellulitis, orbital cellulitis, orbital abscess, subperiosteal abscess, and cavernous sinus thrombosis.

Acute odontogenic infection may spread through tissue planes and venous channels to involve the orbit. The routes of infectious extension may be summarised as follows: (1) The roots of maxillary premolar and molar teeth may lie very close to the maxillary sinus. Maxillary sinusitis may result from extension of maxillary molar or premolar infection or from perforation of the sinus floor during extraction of diseased maxillary teeth. Sinusitis may then extend into the orbit to cause orbital cellulitis.[1] (2) Infection of maxillary incisors or canines may spread through local tissue planes over the maxilla, resulting in swelling of the upper lip, canine fossa, and periorbital tissue. Retrograde spread into the orbit may then occur through the valveless anterior facial, angular, and ophthalmic veins.[5] (3) Infection of anterior maxillary teeth may also spread as a subperiosteal abscess to the anterior surface of the maxilla to involve the orbit.[1] (4) Infection of the posterior maxillary teeth, most commonly the third molar, may spread posteriorly into the pterygopalatine and infratemporal fossae. The infection may then extend into the orbit through the inferior orbital fissure.[1 5 13]

Our cases illustrate 2 of these mechanisms of spread. Patient 1 had an infection of maxillary molar and premolar teeth that spread to the infratemporal space and pterygopalatine fossa. The infection presumably gained access to the orbit through the inferior orbital fissure. A subperiosteal abscess developed in the posterior lateral orbital wall, which subsequently spread within the muscle cone. *Bacteroides melaninogenicus* (subspecies *intermedius*), a gas-forming organism, was cultured from the infratemporal fossa, pterygopalatine fossa, and from the subperiosteal abscess. In patient 2 infection of an anterior maxillary tooth with a root in close proximity to the maxillary sinus resulted in acute pansinusitis and right orbital cellulitis. No organism was recovered from blood or nasal cultures.

Infections of periorbital and orbital tissues are classified according to their location relative to the orbital septum.[14] The orbital septum separates the orbital contents from the lids and acts as a barrier to the spread of infection from the skin into the orbit. Preseptal cellulitis involves the tissues anterior to the septum, whereas orbital cellulitis involves those tissues posterior to the septum. It has been shown that orbital cellulitis may be complicated by orbital or subperiosteal abscesses in more than 20% of cases.[9] A subperiosteal abscess may develop from direct extension of suppuration into the tissue plane between the periosteum and the orbital wall. An orbital abscess may form by the consolidation of infection within the orbit or from the rupture into the orbit of a subperiosteal abscess.

It may be difficult sometimes to distinguish between these entities on clinical grounds alone. All are associated with warm, erythematous, swollen lids with varying amounts of conjunctival chemosis. However, proptosis, restriction of ocular motility, pain on ocular movement, an afferent pupillary defect, decreased visual acuity, disc oedema, choroidal folds, and retinal venous stasis distinguish infections within the orbit from preseptal cellulitis.

It is important to identify cases with orbital or subperiosteal abscess formation, because prompt surgical drainage in these cases is usually necessary to prevent permanent visual loss. Computed tomography is an established radiographic procedure that can aid in the differentiation of these entities.[10 11]

Preseptal cellulitis is characterised on computed tomographic scanning by the presence of inflammation localised in the tissues anterior to the orbital septum without intraorbital disease. Orbital cellulitis can be demonstrated as an obliteration of fat shadows within the muscle cone or the presence of soft tissue swelling within the orbit. Computed tomographic examination of a patient with a subperiosteal abscess shows a mass lesion located between the orbital wall and the displaced periosteum. The periosteal wall of the abscess may at times be more clearly defined with the use of intravenous iodinated contrast medium. An orbital abscess appears as a localised inflammatory mass within the orbital tissues. Gas may be demonstrated within the abscess, arising either from gas-forming bacilli or from a communication of the abscess with an adjacent paranasal sinus. An abscess may be outlined by the use of contrast enhancement.

Computed tomographic scanning proved useful in both of our patients. In case 2, after no improvement was noted with intravenous antibiotic therapy, the computed tomographic scan revealed orbital cellulitis and ruled out an orbital abscess. In case 1 the computed tomographic scan demonstrated a subperiosteal abscess in the posterior lateral orbital wall and an intraorbital abscess with gas. Timely direct drainage of the subperiosteal abscess and decompression of the orbit resulted in resolution of proptosis, recovery of visual acuity, improvement of ocular motility, and return of the visual fields to normal.

Axial computed tomographic scans of the orbit are also of value in delineating the anatomical association among the orbits, the paranasal sinuses, and intracranial structures. Computed tomographic scanning can identify cerebral complications such as cerebritis, brain abscess, and epidural infection. In addition axial views allow comparison of both orbits to detect minimal significant differences. This view is also useful to evaluate proptosis and displacement of the globe, muscle cone, or optic nerve.

Prior to the use of computed tomographic scanning identification of the site of abscess formation was primarily accomplished by localising inflammatory signs and the direction of displacement of the globe.[14] However, these methods have limitations, especially when proptosis is axial. Computed tomographic scanning can precisely localise abscesses, which allows the correct surgical approach to be taken for drainage.

The most frequently isolated organisms in orbital infections in adults include *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Str. pneumoniae*.[14 15] In addition *Haemophilus influenzae* is a very commonly isolated pathogen in children.[16] Other aerobic Gram-negative organisms are rare. A wide variety of anaerobic or microaerophilic organisms, particularly *Bacteroides* species, have been implicated in orbital cellulitis.

The presence of gas in association with orbital infections may aid in the identification of the causative organism. The differential diagnosis of gas-producing organisms includes anaerobic bacteria such as *Clostridia*, *Bacteroides*, anaerobic streptococci, and anaerobic micrococci. Aerobic enterobacteria such as *Proteus*, *Klebsiella*, and *Escherichia coli* can also produce gas.[17 18] In addition defects in the orbital walls produced by infection of the paranasal sinuses may allow air from the respiratory tract into the orbit, simulating gas produced by gas-forming organisms.[19]

Antibacterial therapy should be based on the organisms most likely to be encountered. In cases of orbital infection with associated dental or sinus infection initial treatment with penicillin and a penicillinase-resistant antibiotic is recommended. The therapeutic regimen can be altered when the results of bacterial cultures and tests of antibiotic sensitivities are available.

This work was supported in part by grant PHS HL15168 from the National Heart, Lung, and Blood Institute, Bethesda, MD.

The manuscript was edited by Maxine Gere and typed by Cynthia Gustman.

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British Journal of Ophthalmology, 1982, **66**, 275

Correspondence

Depth perception in strabismus

SIR, In reply to the letter by Cooper and Feldman[1] I must first of all apologise for not referencing all their papers and in particular the Cooper and Warshowsky[2] paper, which was especially relevant to our comment about the Titmus test.

Our only excuse is that the research was specifically aimed at establishing whether squinters are able to use the disparity cue in the normal environment. The Howard-Dolman apparatus allowed us to test this. The measurements taken with the Titmus test and the Frisby test were added to give some clinical relevance to the experimental findings. We did not use any random dot stereograms and made no comments in the paper about them. Their statement at the beginning of the second paragraph is therefore incorrect.

Small-angled strabismics are indeed extremely difficult to find. In order to find the sample reported in this paper we went through the past records of the University's Orthoptics Clinic, and also those of 3 local hospitals. Patients diagnosed as small-angled strabismics were then invited to act as subjects in the research project. All subjects were paid and had their previously diagnosed defect confirmed just prior to the experiment. We are therefore as confident as one ever can be that the diagnoses were correct.

I have looked carefully through all 4 of the Cooper and Feldman articles referenced in their letter, and while I have been able to find a statement in the discussion section of reference 4, pertaining to the existence of line stereopsis in squinters,[3] I can find no reported experimental evidence to support it.

In conclusion, our findings are in agreement with theirs.

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References

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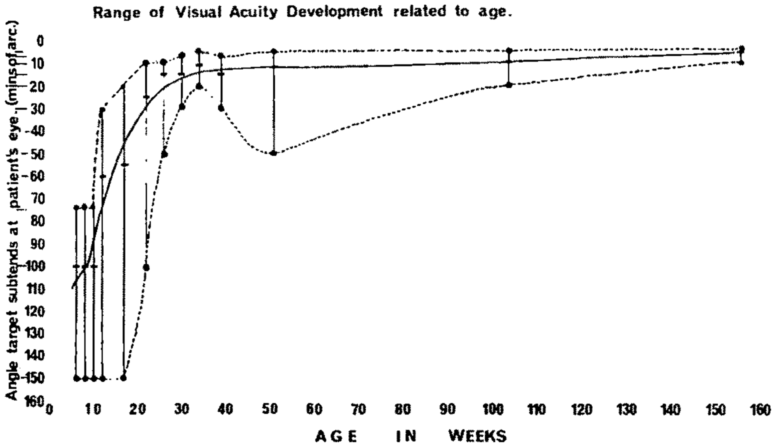
Catford drum

SIR, It is now over 10 years since the original prototype drum was produced to give some guide to visual responses in young babies, and I am delighted that Atkinson *et al.*[1] have been able to use their research facilities for more accurate studies of responses in adults. The original design was for use in the handicapped and very young, where objective results may be the only possible assessment. It was because these results had to be tabulated for the use of paediatricians and for educational school requirements that Snellen equivalents were introduced.



In the article it is interesting to note that the dynamic drum target is compared with a static Landolt C target, and that the ratio of inconsistency is very constant (Table 1) and merits further elucidation. However, the values of below 6/60 in later tables do not give specific detail as would be required to equate with visually disabled children (PL to 6/24), and the Keystone may produce an error of involuntary accommodation, especially in healthy young adult subjects.

Obviously, there is much to be done, and co-operative work with the present authors would be welcomed in order to produce an improved clinical tool for the benefit of assessment of visually handicapped children. The original Development Scale (Fig. 1), in minutes of arc relative to age, may be of interest to readers.

11 Devonshire Place, G. V. CATFORD
London W1N 1PB.

Reference

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Obituary

N. W. Gardener, MRCS, LRCP, DOMS

N. W. Gardener, who was consultant ophthalmic surgeon at Watford and Hemel Hempstead, died on 18 October 1981 at his home at Boxted Farm at the age of 74.

Norman William Gardener was born on 16 September 1907 the eldest of 6 children. He qualified at Guy's Hospital in 1933. After a post as ophthalmic house surgeon at Chesterfield Royal Hospital he became ophthalmic registrar at the Wolverhampton and Midland Counties Eye Infirmary and later ophthalmic registrar at Guy's Hospital. He obtained the DOMS in 1935 and was outpatient officer at Moorfields Hospital prior to his appointment as ophthalmic consultant to Watford General Hospital and West Herts Hospital, Hemel Hempstead. An excellent surgeon who took infinite pains over his patients' problems, both medical and social, he developed a large practice in the Watford area and will be sadly missed. Apart from his ophthalmic work he took a great interest in his farm at Boxted, Hemel Hempstead. Over the last 20 years he was dogged by ill health and had to retire early from his hospital work. However, he did continue for a time working in the practice at Watford as long as he was able. The sad loss of his wife Joan in 1972 was a blow from which he never really recovered, and his active life the last few years had been very limited.

Norman Gardener leaves 4 surviving sons and one daughter and 17 grandchildren, and to them we extend our deepest sympathy. R.S.E.B.

Notes

Retinal vascular and macular disorders

The Retinal Vascular Center of the Wilmer Institute will hold its 12th anniversary meeting at Sun Valley, Idaho, on 12–16 July 1982. The conference is entitled 'Diagnosis and Management of Retinal Vascular and Macular Disorders.' Topics will include treatable macular disorders, argon and krypton laser photocoagulation, pigmentary retinopathies, diabetic retinopathy, vitrectomy, macular degeneration, toxoplasmosis, lupus retinopathy, immunology and ocular inflammation, cystoid macular oedema, uveitis syndromes, and complications of cataract surgery. The format will include lectures, free papers, and open discussion between faculty and course participants. Sessions daily from 8.00 to 12.30 pm. Registration fee $425.00. For further information: Program Co-ordinator, Office of Continuing Education, Johns Hopkins University, 720 Rutland Avenue, Turner 22, Baltimore, Maryland 21205, USA.

Cosmetic surgery

The Department of Ophthalmology and the Page and William Black Postgraduate School of Medicine of the Mount Sinai School of Medicine will hold a postgraduate course on 'Cosmetic surgery of the aging eye' on 18–19 June 1982. Further details from The Director, Page and William Black Postgraduate School of Medicine, Mount Sinai School of Medicine, 1 Gustave L. Levy Place, New York, NY 10029, USA.

Lacrimal surgery course

The eighth annual Boston lacrimal surgery course will be held at the Colonnade Hotel, Boston, Mass, USA, on 3–4 June 1982. Further details from the Boston Eye Research Institute, 20 Hope Avenue, Suite 106, Waltham, Mass 02154, USA.

The Treacher Collins prize essay

Under this title the Council of the Ophthalmological Society of the United Kingdom has instituted a prize of £200 awarded triennially for the best essay submitted on a subject selected by the council. The prize is open to qualified medical practitioners of any nationality. The essay must be written in the English language. The subject for the next award of the prize is 'Developments in the Treatment of Cataract.' The winning essay may be published in the *Transactions of the Ophthalmological Societies of the United Kingdom* if the Council so desires. The closing date for sending in essays for this award is 31 July 1982. Essays should be submitted in triplicate to the Honorary Secretary, Opthalmological Society of the United Kingdom, Royal College of Surgeons, 35/43 Lincoln's Inn Fields, London WC2A 3PN. No name should be on any essay, but a distinguishing pseudonym or quotation on a sealed envelope containing the candidate's name and address should accompany the essay.

Glaucoma group travel fellowship

This fellowship, sponsored by Merck Sharp and Dohme, is available to medical graduates and nonmedical scientists resident in the United Kingdom or Eire. It will assist a visit to a hospital or research centre during the academic year starting 1 October 1982 and will be equivalent to £1500. Its purpose is to enable the successful applicant to gain experience and knowledge in pursuit of a specific research project related to glaucoma. It may be held concurrently with other awards. Applicants should send a curriculum vitae with information on their research project and details of their proposed visit (preferably with confirmation from the centre(s) to be visited) to: Dr S. Nagasubramanian, Glaucoma Group Secretary, Glaucoma Unit, Moorfields Eye Hospital, City Road, London EC1. The closing date for applications is 31 May 1982, and the successful candidate will be informed by 31 July 1982.

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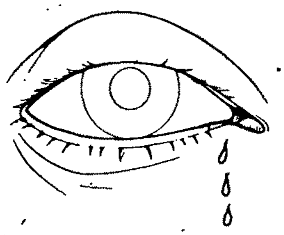

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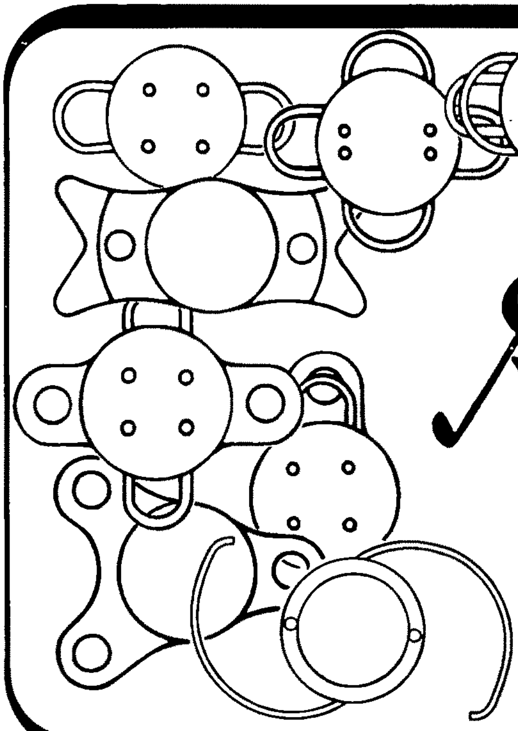
In addition to the above Annual Fellowship there are minor Awards to provide suitable applicants with contributions towards their expenses to attend courses in ophthalmology and related subjects in the U.K. or abroad.

Applications for awards are now invited from Consultant Ophthalmologists, Senior Registrars about to take up consultant appointments, and any other suitable applicants. The Trustees usually meet to consider applications in April, July and November each year, and applications for awards should normally be received in time for these meetings by the end of February, May and September.

Further information and applications forms may be obtained from:

The Secretary, Keeler Award,
Arthur Young McClelland Moores & Co.,
Rolls House, 7 Rolls Buildings,
Fetter Lane, London, EC4A 1 NH.



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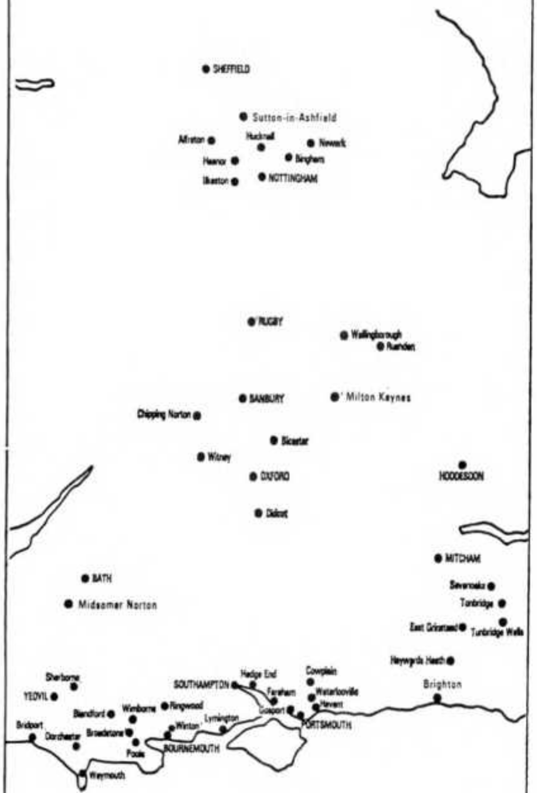

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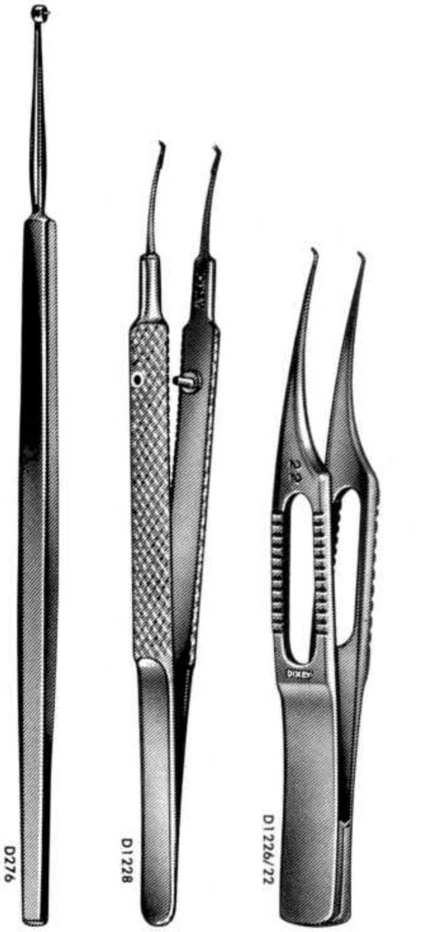

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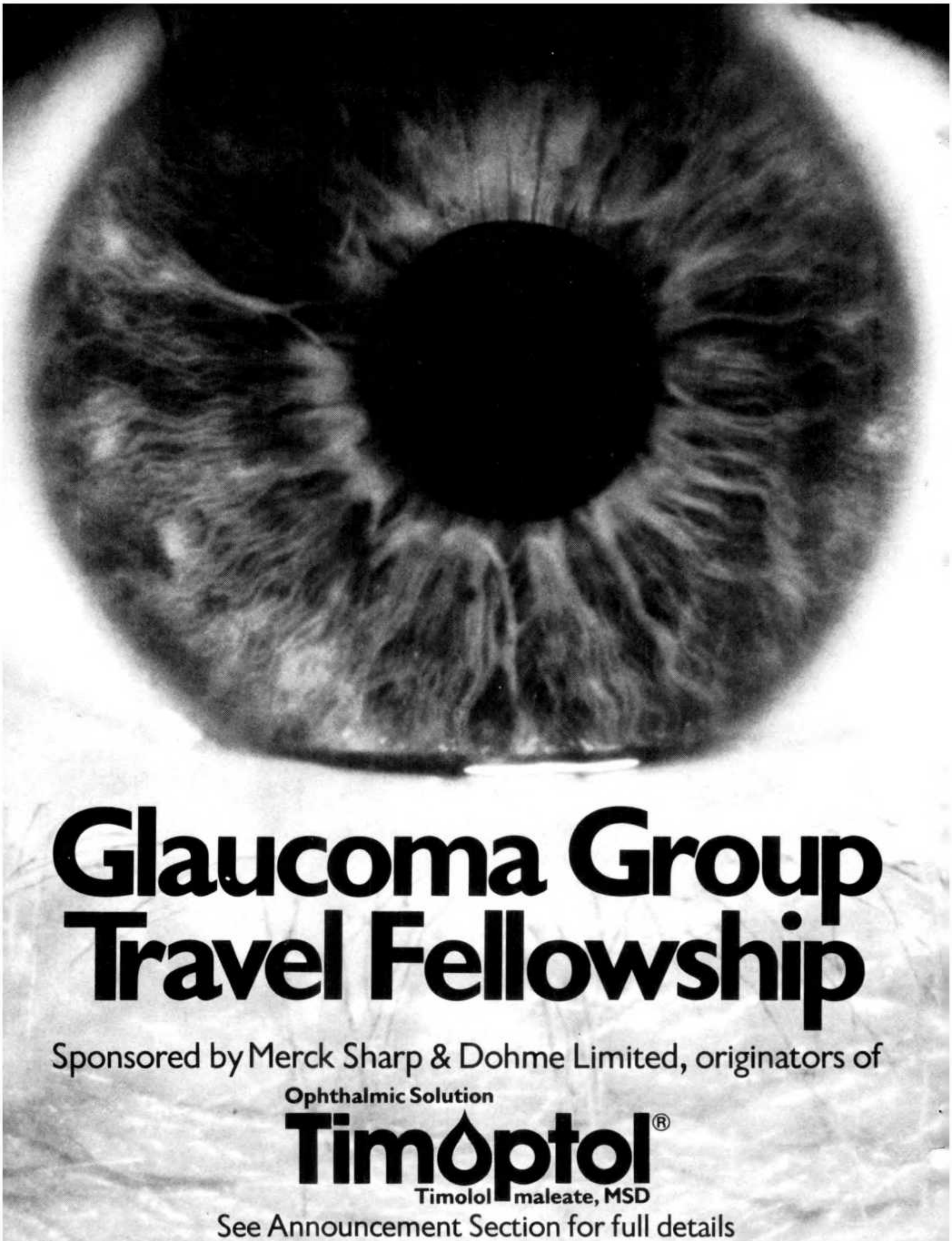

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Published by British Medical Association, Tavistock Square, London WC1H 9JR.
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British Journal of Ophthalmology April 1982 Vol. 66 No. 4

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ASTM CODEN BJOPAL 66 (4) 213-276 (1982)

ISSN 0007-1161

British Medical Association Tavistock Square London WC1H 9JR

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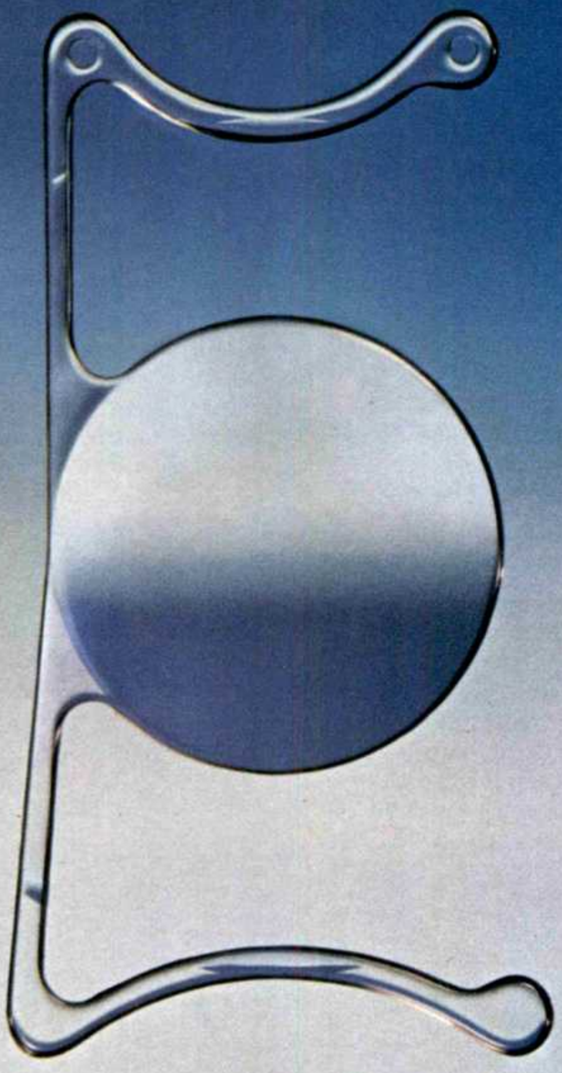

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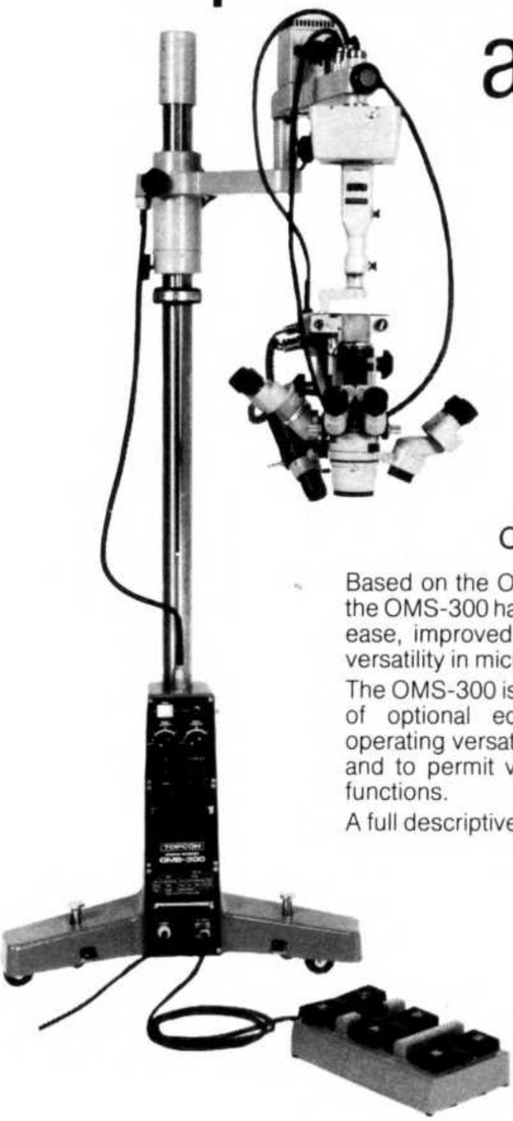

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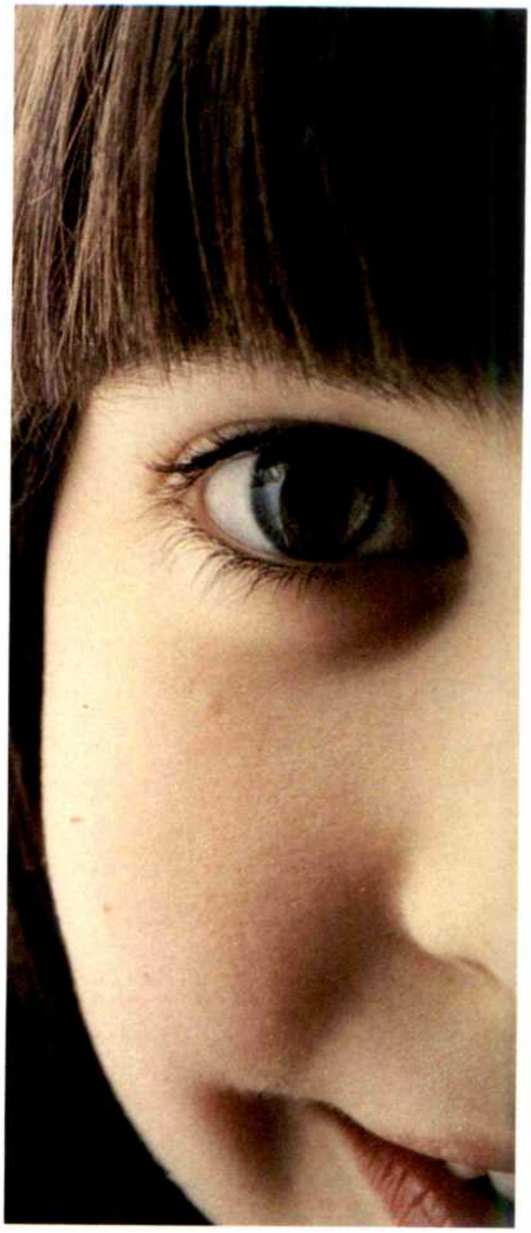

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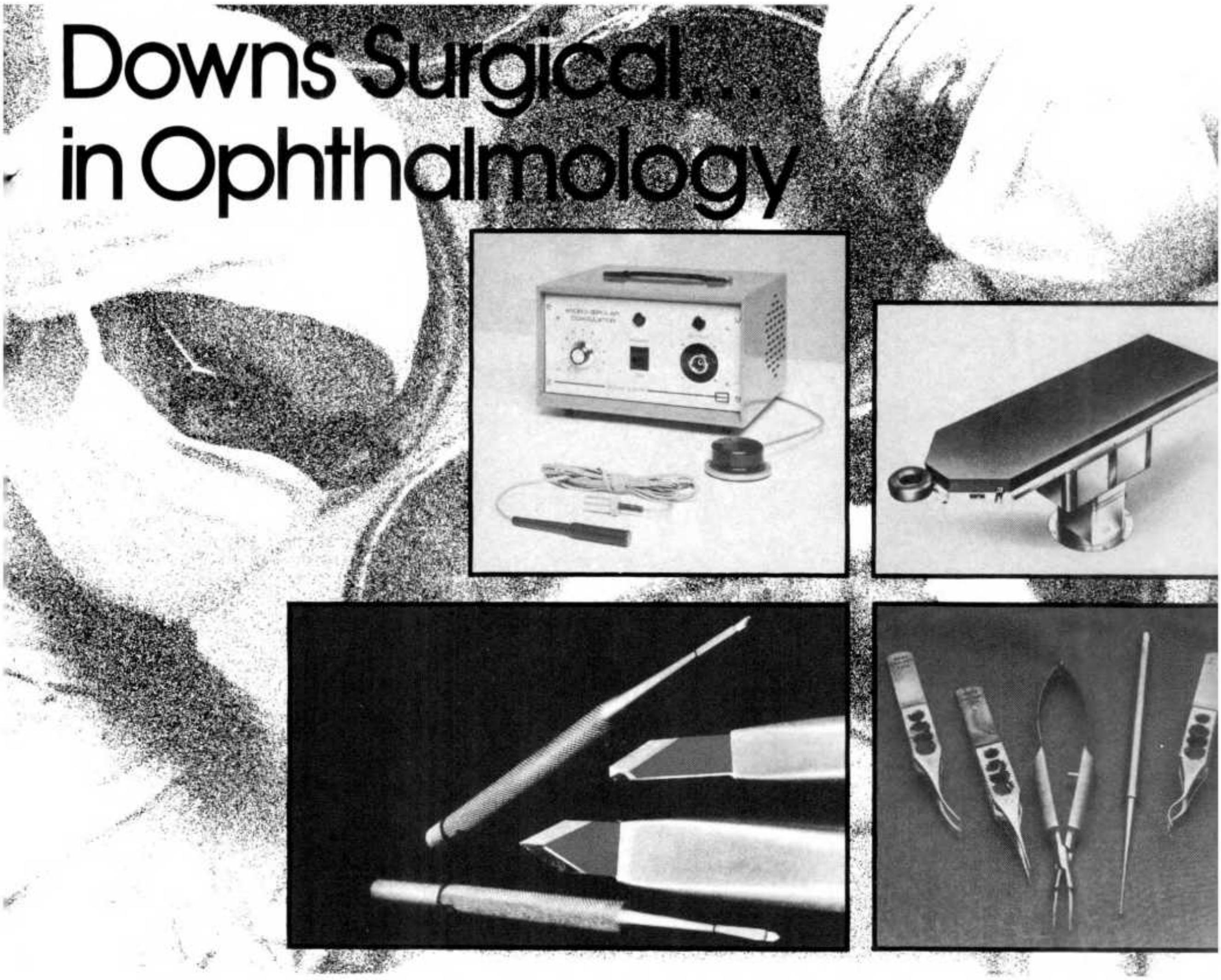

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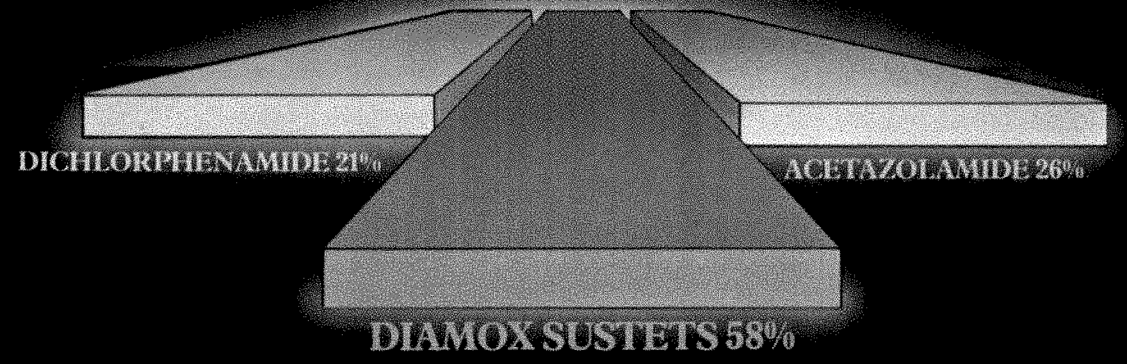

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British Journal of Ophthalmology, 1982, **66**, 277–279

Analysis of HLA antigen association with proliferative diabetic retinopathy

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SUMMARY One hundred and thirteen patients with insulin dependent diabetes mellitus for at least 15 years were typed for 22 HLA antigens of the A and B series. Fifty-six patients had severe bilateral proliferative retinopathy and 57 had no retinopathy. There was no statistical difference in frequency of HLA antigens between the 2 groups of diabetic patients. There was a significantly higher frequency of HLA B15 and a significant lower frequency of HLA B14, B17 in the combined diabetic groups than in a control population of 200 normal blood donors.

Proliferative diabetic retinopathy is a major cause of blindness in insulin dependent diabetics. Duration of the disease and hyperglycemia[1] are important factors influencing development of retinopathy. However, a proportion of patients with long-standing diabetes are found without visible retinopathy.[2] Pyke and Tattersall[3] studied the prevalence of diabetic retinopathy in identical twins and suggested that genetic factors may exist which protect or predispose diabetics to retinopathy. Barbosa *et al.*[4] and Cudworth *et al.*[5] studied histocompatibility antigen frequencies in relation to diabetic eye disease and detected a positive association with HLA B15 and a negative association with HLA B7. This association if confirmed will be helpful in identifying diabetic patients susceptible to proliferative retinopathy.

We studied the frequency of 22 histocompatibility antigens of the A and B series in 2 groups of insulin dependent diabetics which differed only in the presence or absence of proliferative retinopathy.

Patients and methods

Two groups of patients were selected for study from patients attending the diabetic eye clinic at the Royal Victoria Hospital and were matched for sex, age, duration of diabetes, and age at onset of diabetes. One group of 57 insulin dependent diabetic patients had had the disease for at least 15 years (mean 27·0 years) without ophthalmoscopic evidence of background or proliferative retinopathy. The age at onset of diabetes was less than 40 years in every patient (mean 20·3 years). The second group consisted of 56 diabetic patients with severe bilateral proliferative retinopathy treated by panretinal laser photocoagulation. All these patients had been insulin dependent diabetics for at least 15 years (mean 26·2 years) and had a mean age at onset of 18·2 years. Two hundred normal blood donors resident in Northern Ireland were used as a control.[6]

The diabetic patients and control population were typed for 22 HLA antigens of the A and B series by means of a standard 2-stage microlymphocytotoxicity test at 22°C. The results were analysed statistically by the method described by Edwards.[7]

Results

Table 1 shows the frequency of HLA antigens in the 2 diabetic groups and control population. The 2 groups of diabetic patients were compared, and the total chi-square value was 13·65 with 30 degrees of freedom. This is not significant ($p>0·10$), so we cannot infer that there is any difference between the 2 groups of diabetic patients in terms of HLA antigens.

All the diabetics were compared with the control group, and the total chi-square value was 46·38 with 21 degrees of freedom, which is statistically significant ($p<0·005$). HLA types B14, B15, and B17 were the major contributors. Their combined chi-square value

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Table 1 *Frequency of HLA antigens in the diabetic and control groups*

HLA antigen		*Control (n=200)*		*Diabetic group proliferative retinopathy (n=56)*		*Diabetic group no retinopathy (n=57)*		*Total diabetic (n=113)*	
		No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
A	1	86	43·0	28	50·0	21	36·8	49	43·3
	2	91	45·5	26	46·4	30	52·6	56	49·6
	3	53	26·5	14	25·0	14	24·6	28	24·8
	9	31	15·5	10	17·9	8	14·0	18	16·0
	10	20	10·0	3	5·3	3	5·2	6	5·3
	11	28	14·0	7	12·5	7	12·3	14	12·4
	28	10	5·0	3	5·4	7	12·3	10	8·8
	29	16	8·0	2	3·6	6	10·5	8	7·1
B	5	13	6·5	3	5·4	0	0	3	2·7
	7	67	33·5	14	25·0	11	19·3	25	22·1
	8	69	34·5	28	50·0	24	42·1	52	46·0
	12	54	27·0	10	17·9	15	26·3	25	22·1
	13	5	2·5	3	5·4	1	1·8	4	3·5
	14	30	15·0	3	5·3	2	3·5	5	4·4
	15	9	4·5	9	16·1	11	19·3	20	17·7
	17	18	9·0	1	1·8	1	1·8	2	1·8
	18	16	8·0	6	10·7	6	10·5	12	10·6
	22	8	4·0	4	7·1	4	7·0	8	7·1
	27	11	5·5	3	5·3	5	8·8	8	7·1
	35	16	8·0	4	7·1	2	3·5	6	5·3
	40	20	10·0	7	12·5	12	21·1	19	16·8

was 26·7 with 2 degrees of freedom. Without selection this would be significant with $p<0·0005$. If the probability is multiplied by $n-3$,[7] the significance is $p<0·01$.

Our results indicate that all diabetics are most likely to have HLA B15 and less likely to have HLA B14 and B17. There is no difference in HLA frequency between the 2 groups of diabetic patients.

Discussion

Several reports suggest a genetic predisposition to diabetic retinopathy. Barbosa *et al.*[8] found an association between HLA antigens A1 and B8 with severe diabetic microangiopathy. Larkins *et al.*[9] report an association between the pattern HLA B8 without HLA A1 and severe proliferative retinopathy, although we were unable to confirm this observation in a previous report.[10] Barbosa *et al.*,[4] Bertrams and Spitznas,[11] and Cudworth *et al.*[5] found that patients with proliferative retinopathy have a strong association with HLA B15, and Barbosa *et al.*[4] also observed that diabetic patients with proliferative retinopathy were less often positive for HLA B7. However, Becker *et al.*,[12] Moller *et al.*,[13] and Deckert *et al.*[14] did not detect a significant difference in HLA antigen frequency between juvenile onset diabetics with and without retinopathy. In the present study we were unable to detect a difference in HLA antigen frequency between 2 groups of juvenile onset diabetics which differed only by the presence of severe proliferative retinopathy or no visible retinopathy.

We found a significant increase in the frequency of HLA B15 in the combined diabetic group which corresponds with other reports.[8 12 13 15–17] A positive association between juvenile onset diabetes and HLA B8 was reported by Cudworth and Woodrow.[15] We found a high frequency of HLA B8 (46%) in our combined diabetic groups, but this was not significantly different from that in the control group of 34·5%. The control group frequency of HLA B8 is high in comparison with results published for other populations apart from a frequency of 34·8% detected by Reen and O'Regan[18] in a Southern Irish population. The high frequency of HLA B8 in our control group may mask an association with juvenile onset diabetes which others have found. There was a reduced frequency of HLA B14 and B17 in our combined diabetic group, which has not been reported previously.

We acknowledge the assistance of the Tissue Typing Laboratory at the Belfast City Hospital.

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British Journal of Ophthalmology, 1982, 66, 280–285

HLA antigens and other risk factors in the development of retinopathy in type 1 diabetes

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SUMMARY Factors possibly influencing the development of diabetic retinopathy were studied in 112 randomly selected type 1 diabetics having no or minimal retinopathy (group A) and in 82 type 1 diabetics with known severe diabetic retinopathy. The latter comprised those with severe background retinopathy (group B, n=17) and those having proliferative retinopathy without (group C, n=38) and with (group D, n=27) diabetic nephropathy. Nonretinopaths (group A) were of similar sex ratio, body weight, and age at diagnosis of diabetes but had been diabetic longer ($p<0·001$) and were thus older ($p<0·001$) than retinopaths (groups B-D). The distribution of HLA antigens of the A, B, and C loci was similar in nonretinopaths and retinopaths with the exception that HLA B7 showed a reduced ($p<0·05$) prevalence in the retinopaths (6% versus 17%) and was singularly underrepresented in group D, where no patients had this antigen. Mean postprandial plasma glucose and HbA_1 concentrations were higher ($p<0·01$ and $p<0·001$) and cigarette smoking was more prevalent ($p<0·01$) in the retinopathy groups B-D than in group A. Systolic and diastolic blood pressures were similar in groups A-C, with higher ($p<0·001$) values only in group D. There was no association between insulin antibody binding in the serum or measurable plasma C-peptide immunoreactivity and retinopathy status. The risk of development of diabetic retinopathy in type 1 diabetes may be related to HLA-associated genetic factors and to cigarette smoking.

In order to evaluate the possible factors which may influence the incidence, severity and progress of retinopathy in type 1 diabetics we have examined the frequencies of the HLA antigens of the A, B, and C loci, selecting only those diabetics who had either developed severe diabetic retinopathy or exhibited an apparent immunity to the development of other than very mild background diabetic retinopathy. Since duration of diabetes is possibly the most important determinant of the development of diabetic retinopathy, we have taken particular care to select retinopaths of short duration of diabetes and nonretinopaths of long duration of diabetes. In addition to considering HLA antigen frequencies we have compared the 2 groups of diabetics in respect of postprandial plasma glucose concentration, total glycosylated haemoglobin (HbA_1), insulin antibody binding by serum, prevalence of diastolic and systolic hypertension, and smoking history. Finally, we have shown that all subjects studied were type 1 diabetics by confirming an absent or only just measurable postprandial C-peptide concentration in the plasma. We thus avoided the risk of inadvertently including subjects with 'maturity onset diabetes of the young' in the group of nonretinopaths.

Patients and methods

PATIENTS

All 194 diabetics studied attended the Diabetic and Dietetic Department, Royal Infirmary, Edinburgh, having presented with clinical features of type 1

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diabetes before the age of 35 years and having been treated with insulin from the outset.

Nonretinopaths. One hundred and twelve unrelated diabetics (49 males, 63 females) were randomly selected from a cohort of patients who are the subject of a long-term prospective study of the development of retinopathy. All such patients were known to have been diabetic for at least 15 years, in which time they had no ophthalmoscopic evidence of diabetic retinopathy.

Retinopaths. Seventy-three unrelated diabetics (44 males, 29 females) with severe background or proliferative retinopathy were studied representing all available type 1 diabetics of duration of diabetes less than 25 years who had been referred to the Princess Alexandra Eye Pavilion, Edinburgh, during 1972–8 for treatment of diabetic retinopathy, from the Diabetic and Dietetic Department, Royal Infirmary, Edinburgh. In order to correct for the male preponderance found in this group of patients a further 9 female retinopaths were included whose proliferative retinopathy was diagnosed in 1979–80.

Nondiabetic controls. One hundred blood donors (50 males, 50 females) were HLA typed.

METHODS

All diabetics' fundi were examined ophthalmoscopically through dilated pupils by one observer (B.F.C.), who assessed the corrected near visual acuity (by standard reading test types) in each patient together with blood pressure in the sitting position after resting quietly for at least 5 min. Patients receiving antihypertensive treatment whose diastolic and/or systolic pressures had previously been recorded as greater than 85 and 155 mmHg, respectively, were identified.

Past and present degrees of proteinuria were assessed by Multistix (Ames Co.).

A questionnaire regarding cigarette smoking habits and family history of diabetes was completed by each diabetic.

A single venous blood sample was withdrawn from each diabetic 1–2 hours after breakfast and was analysed in the following manner. HLA typing was carried out in 104 (93%) nonretinopaths and in all retinopaths (n=82) and nondiabetic controls (n=100). Diabetics and controls were typed concurrently by the standard National Institutes of Health (NIH) lymphocyte cytotoxicity technique against a panel of 120 antisera defining the following locus A, B, and C specificities: HLA A 1, 2, 28, 3, 9 (23, 24), 10 (25, 26), 11, 19, 29, 30, 31, 32, 33. HLA B 5, 7, 8, 12, (44, 45), 13, 14, 15, 16, (38, 39), 17, 18, 21, (49, 50), 22, 27, 35, 37, 40, BW4 and BW6. HLA C CW3 CW4.

In all (n=112) nonretinopaths and 79 (96%) retinopaths the following investigations were carried out. HbA_1 was measured by a modification[1] of the column chromatographic technique of Kynoch and Lehmann.[2] Reversible and stable forms of HbA_1 were not separated by dialysis of red cells.[3] Between-batch precision, estimated by repeat analysis of specimens from patients, showed a coefficient of variation (CV) of 3·5%. The normal range in non-diabetics in our laboratory is 5·2–8·4%.

Plasma glucose was estimated by a standard glucose oxidase method.[4]

The binding of ^{125}I-labelled beef insulin by serum samples was determined by a method using polyethylene glycol separation.[5] The nonspecific binding did not exceed 1·5%, and all samples were analysed in one assay, with precision of 2·5% (CV) across the range. Results are expressed as percentage of labelled insulin bound.

C-peptide was measured by radioimmunoassay by a modification of the method described by Heding.[6] Antibody M1230 raised against human C-peptide was used at an initial dilution of 1/25 000. The detection limit of the assay was 0·04 nmol/l (calculated as 2 standard deviations (SD) from 0). Cross-reaction with human proinsulin is 11% on a molar basis. The interassay coefficient of variation was 6%. Antibody M1230, human C-peptide standard, and iodinated tyrosylated C-peptide were gifts of the Novo Research Institute, Copenhagen, Denmark.

Comparison of groups was by Wilcoxon rank sum, Kruskal-Wallis, or chi-square tests as appropriate, and relationships between variables were tested by Kendall rank correlation (τ).

Results are presented as mean±(SD) unless otherwise stated.

Results

Thirty-one nonretinopaths (28%) had minimal diabetic venous changes and/or less than 5 microaneurysms in each fundus, while the remaining 81 (72%) nonretinopaths had no ophthalmoscopic evidence of diabetic retinopathy. All 112 diabetics were assigned to group A and hereafter continue to be referred to collectively as nonretinopaths. Seventeen retinopaths (8 males, 9 females; group B) had severe background retinopathy as evidenced by widespread microaneurysms, blot, flame, or subhyaloid haemorrhages with or without hard or soft exudates but did not exhibit and had not previously exhibited new vessel formation. Sixty-five retinopaths (37 males, 28 females) had proliferative diabetic retinopathy and were divided into patients without (18 males, 20 females; group C) and with (18 males, 9 females; group D) diabetic nephropathy (vide infra).

Table 1 *Clinical characterisation of nonretinopaths and retinopaths*

	Nonretinopaths	*Retinopaths*		*Significance*
		Severe background	*Proliferative*	*Nonretinopaths vs. retinopaths*
Number of subjects	112	17	65	—
Sex (% male)	44	47	55	NS
Age (years)	46±14	34±8	37±11	p<0·001
Duration of diabetes at time of study (years)	26±10	12±4	21±7	p<0·001
Duration of diabetes at diagnosis of severe background and proliferative retinopathy (years)	—	12±3	18±6	—
Insulin regimen: daily dose (units)	59±23	60±28	64±30	NS
*Receiving conventional beef insulin (%)	72	65	71	NS
Receiving once daily insulin (%)	56	47	52	NS
†Ideal body weight (%)	100±13	103±14	99±13	NS
Diabetic first-degree relative (%)	21	12	26	NS
Visual acuity: better eye	5·4±1·6	6·3±4·6	8·3±10·6	—
worse eye	7·2±7·0	7·0±5·1	23·1±20·3	—
§Proteinuria grade 0	104	16 (1)	32 (1)	
1	6	0	6	
2	2	0	17 (2)	
3	0	1 (1)	10 (7)	

*Patients not on conventional beef insulin had been converted to highly purified pork insulin up to 3 years prior to time of study.
†Metropolitan Life Assurance Tables, 1959.
§Proteinuria grade: 0=no proteinuria; 1=intermittent proteinuria; 2=persistent proteinuria; 3=nephrotic syndrome—patients with raised creatinine in parenthesis.
Results are expressed as mean±SD.

Owing to the method of patient selection nonretinopaths had been diabetic longer ($p<0\cdot001$) and were older ($p<0\cdot001$) than retinopaths, but there was no significant difference in sex ratio, daily insulin dose, percentage of ideal body weight, insulin regimen, or family history of diabetes (Table 1) between nonretinopaths and retinopaths. The visual acuity in each eye of proliferative retinopaths was worse ($p<0\cdot001$ and $<0\cdot001$) than that of nonretinopaths (Table 1).

The prevalence of proteinuria and renal failure (serum creatinine >150 µmol/l) in nonretinopaths and retinopaths is also shown in Table 1. Patients with persistent proteinuria or the nephrotic syndrome (without evidence of other than diabetic renal disease) are defined as having diabetic nephropathy.

HLA TYPING

Table 2 shows the distribution of HLA antigens in the subjects studied which are reported to be over- or

Table 2 *HLA antigen frequencies (%) in study group*

HLA	*Diabetic groups*						*Controls*	*Significance*			
	A	*B*	*C*	*D*	*B+C+D*	*A+B+C+D*		*(1)*	*(2)*	*(3)*	*(4)*
n=	*104*	*17*	*38*	*27*	*82*	*186*	*100*				
A1	48	47	50	56	51	50	31	NS	NS	p<0·01	NS
B7	17	12	8	0	6	12	26	NS	p<0·05	p<0·01	p<0·05
B8	46	47	58	55	55	50	23	NS	NS	p<0·001	NS
B15	21	6	13	22	15	18	10	NS	NS	NS	NS
B18	4	18	8	15	12	7	5	NS	NS	NS	NS
A1+B8	42	29	47	52	45	43	18	NS	NS	p<0·001	NS
B8−A1	4	18	10	4	10	6	5	NS	NS	NS	NS
B8+B15	6	6	5	11	7	6	2	NS	NS	NS	NS

Significance: (1) Among groups B, C, and D. (2) Groups B, C, and D vs. group A. (3) Groups A, B, C, and D vs. controls. (4) Group A vs. Groups C and D.

Group A=nonretinopaths. Group B=severe background retinopaths. Group C=proliferative retinopaths without diabetic nephropathy. Group D=proliferative retinopaths with diabetic nephropathy.

Table 3 *Risk factors in nonretinopaths and retinopaths*

	Diabetic groups				*Overall comparison*
	A	*B*	*C*	*D*	
Number of subjects	112	17	36	25	
HbA$_1$ (%)	12·1±1·8	15·0±2·5	13·3±2·1	13·6±2·5	p<0·001
Postprandial plasma glucose (mmol/l)	12·6±5·8	18·7±8·2	14·9±8·2	17·1±9·9	p<0·05
Beef insulin antibody binding (%)	23·2±16·1	17·2±13·0	21·7±18·8	16·4±12·4	NS
Plasma C-peptide* (nmol/l)	0·08±0·04 (0·04–0·29)	0·09±0·04 (0·04–0·17)	0·10±0·13 (0·04–0·47)	0·05±0·06 (0·04–0·06)	NS
Diastolic hypertension (%) (>85 mmHg)	14	0	11	56	p<0·001
Systolic hypertension (%) (>155 mmHg)	12	6	3	41	p<0·001
Smoking history: smoking at time of study (%)	38	59	54	69	p<0·05
number of cigs/day†	20±12	21±8	21±10	24±11	NS
years smoked†	21±10	13±4	18±8	17±7	p<0·05

Results expressed as mean±SD, or range (in parentheses).
*In patients with measurable C-peptide concentration only.
†Smokers only.

underrepresented in type 1 diabetics in this or previous studies. HLA A1 and B8 were significantly (p<0·01 and <0·001) overrepresented (relative risks=2·18 and 3·34) and B7 significantly (p<0·001) underrepresented (relative risk=0·40) in all diabetics (groups A-D) in comparison with controls. The combination of A1 and B8 was more frequently (p<0·001) found in all diabetics (groups A-D) than in controls (relative risk=3·51).

The frequency of HLA B7 was greater (p<0·05) in nonretinopaths (group A) than in all retinopaths (groups B-D) and greater (p<0·05) than in diabetics with proliferative retinopathy (groups C and D). None of the 27 patients in group D exhibited HLA B7. The frequencies of inferred homozygosity of HLA B7 and B8 were 3% and 15% in diabetic nonretinopaths, 0% and 15% in diabetic retinopaths, and 2% and 1% in nondiabetic controls.

HbA$_1$ AND POSTPRANDIAL PLASMA GLUCOSE CONCENTRATIONS

Table 3 shows the mean HbA$_1$ and postprandial plasma glucose values of diabetics in groups A-D. There was no significant difference between plasma glucose values of patients in groups B-D whose overall mean value (16·4±8·8 mmol/l) was significantly higher (p<0·01) than that of patients in group A (12·6±5·8 mmol/l). Similarly, the mean HbA$_1$ value of patients in groups B-D (13·8±2·4%) was significantly higher (p<0·001) than that (12·1±1·8%) of patients in group A. There was a significant correlation between plasma glucose and HbA$_1$ when retinopaths and nonretinopaths were considered together (τ=0·48, p<0·001) or separately (τ=0·46, p<0·001; τ=0·22, p<0·01). The relationship between plasma glucose and HbA$_1$ was similar in diabetics with and without a raised serum creatinine concentration. There was no significant relationship between HbA$_1$ or plasma glucose and any HLA antigen when considering retinopaths or nonretinopaths. There was no significant relationship between visual acuity and HbA$_1$ or plasma glucose concentration.

Current smokers had a higher mean HbA$_1$ level than nonsmokers (13·2 versus 12·4%; p<0·05), but this is largely accounted for by the higher proportion of smokers among retinopaths. The mean HbA$_1$ of smokers within each of the groups A-D, while significantly higher than that of nonsmokers, is not significantly so in any group.

INSULIN ANTIBODY BINDING

The mean level of insulin antibody binding was not found to differ significantly among patients of groups A-D (Table 3). However, insulin antibody binding correlated significantly with age at study (τ=0·18, p<0·001) and duration of diabetes (τ=0·16, p<0·01). Mean insulin antibody binding in patients taking once daily insulin (25·4±16·8%) was higher (p<0·001) than in those taking twice daily insulin (16·7±14%), while patients taking conventional beef insulin had higher (p<0·001) insulin antibody binding (23·8±15·9%) than those taking highly purified pork insulin (15·6±15·2%). There was no significant relationship between insulin antibody binding and daily insulin dose or plasma C-peptide concentration. Wilcoxon rank sum tests show mean insulin antibody binding to be lower (p<0·01) in HLA B8 positive diabetics (18·2%) than in HLA B8 negative diabetics (25·0%) and to be higher (p<0·05) in HLA B15 positive diabetics (27·1%) than in HLA B15 negative diabetics (20·4%). The association between B15 and high insulin antibody binding was independent of the association between B8 and low insulin antibody binding. Mean insulin antibody binding was not significantly different in B7 positive (26·9%) and negative diabetics (20·8%).

C-PEPTIDE

None of the nonretinopaths studied had a plasma C-peptide concentration greater than 0·29 nmol/l. No significant difference was observed in the frequency with which a measurable C-peptide concentration was found in patients of groups A, B, C, and D (30, 47, 25, and 13%). Table 3 shows that the mean plasma C-peptide concentration was not significantly different within groups A-D.

BLOOD PRESSURE

There was no significant difference in the prevalence of systolic or diastolic hypertension (>155 and >85 mmHg) in patients of groups A-C (Table 3). However, the prevalences of systolic and diastolic hypertension in group D (41 and 56%) were significantly greater ($p<0·001$ and $<0·001$) than in groups A-C (10 and 12%).

SMOKING

Table 3 shows the proportions of patients in groups A-D who were smoking cigarettes at the time of study and provides details of daily number of cigarettes smoked and duration of smoking in past and present smokers. Although retinopaths (groups B-D) included more ($p<0·01$) smokers (60%) than nonretinopaths (38%), this difference was mainly accounted for by the high prevalence of smoking in group D (69%), being significantly greater ($p<0·05$) than in the other 3 groups of diabetics (44%). These differences were not accounted for by the age differences in patients in groups A-D. There was no significant difference between the prevalence of smoking in patients of groups B and C combined (56%) and that of patients in group A or group D. The significantly longer smoking history in group A is presumably due to the greater mean age of patients in this group.

Discussion

A relationship between diabetic microangiopathy and an HLA antigen (or antigens) of the A, B, and/or C loci has been proposed by several authors,[7-14] whose findings are, however, contradictory owing to the heterogeneity of populations under consideration, the small numbers of patients studied, together with the absence or lack of adequate control data. Barbosa *et al.*[14] reported a comparison of HLA antigen frequencies in large numbers of type 1 diabetics (aged less than 40 years at diagnosis of diabetes) with and without proliferative retinopathy. The frequency of B7 was significantly lower in proliferative retinopaths (7%) than in diabetics without proliferative retinopathy (20%), and our own findings are remarkably consistent (5% in proliferative retinopaths versus 17% in nonretinopaths.) None of our 27 patients with proliferative retinopathy and diabetic nephropathy (group D) were B7 positive. A similar underrepresentation of HLA B7 was noted in type 1 diabetic proliferative retinopaths by Standl *et al.*[15] Nevertheless we must concede that the difference in frequency of B7 between proliferative retinopaths and nonretinopaths is modest, that it has not been noted in other studies, and that the aetiology of the putative protective influence of B7 remains obscure. We could not demonstrate a significant relationship between B7 and insulin antibody binding, although we have confirmed the association between high insulin antibody binding and the B15 positive, B8 negative genotype.[16-18] Retinopaths and nonretinopaths had similar insulin antibody binding by serum in accordance with some[12] but not all[19] previous studies. It remains to be seen whether HLA D/DR typing will clarify the issue concerning a possible genetic predisposition to diabetic microangiopathy. Preliminary data[20 21] suggest there is an association between HLA DR4 and diabetic retinopathy. The weak association between retinopathy and absence of HLA B7 may be the consequence of a yet stronger relationship between retinopathy and DR4.

We have shown retinopaths to have significantly higher HbA_1 and plasma postprandial glucose concentrations than nonretinopaths. Our findings are therefore in accordance with those of Schanzlin *et al.*[22] and West *et al.*[23] in type 1 and 2 diabetics respectively. These observations have little bearing on the controversial issue concerning the relationship between long-term diabetic control and the aetiology of diabetic microangiopathy. However, it is interesting to note that the glycaemic control of nonretinopaths is not particularly good, albeit better than that of the retinopaths.

Systolic hypertension has been shown[24] to precede the development of exudative retinopathy in middle-aged diabetic Pima Indians (type 2 diabetics). In the present study neither systolic nor diastolic hypertension was commonly found in type 1 diabetics, most of whom were aged less than 50 years, unless accompanied by diabetic nephropathy. In particular, the prevalence of hypertension was no higher in retinopaths without accompanying nephropathy than in nonretinopaths. It therefore seems likely that hypertension is not a major aetiological factor in the development of severe diabetic retinopathy in type 1 diabetics. We have shown a strong relationship between hypertension and the association of proliferative retinopathy with diabetic nephropathy. While it seems probable that diabetic nephropathy was responsible for the development of hypertension in most cases, we cannot discount the possibility that hypertension was causally related to the development of nephropathy, or even retinopathy, in those patients with underlying diabetic nephropathy.

The present study confirms smoking to be more prevalent among retinopaths than nonretinopaths and is thus in accordance with the findings of Paetku *et al.*[25] However, this difference appears to be due to the remarkably high prevalence of smoking in proliferative retinopaths who have diabetic nephropathy. This finding is in agreement with the observations of Christiansen,[26] who reported heavy smoking to be a characteristic of diabetic nephropaths.

The present study suggests that the risk of development of diabetic microangiopathy is related not only to HLA associated genetic factors but also to cigarette smoking.

The authors gratefully acknowledge the skilled technical assistance provided by Judith Matthews, Margaret Sinclair, Dr A White, and C. Darg. We are also indebted to Miss L. Veitch for her invaluable secretarial assistance. The authors also gratefully acknowledge financial support provided by the British Diabetic Association. A.B.K. was further supported by a grant from Nordisk Insulin Laboratories.

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British Journal of Ophthalmology, 1982, **66,** 286–289

Peripheral retinal haemorrhages in long-duration insulin-dependent diabetes with minimal background retinopathy

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SUMMARY Eight long-standing, well controlled insulin-dependent diabetics with little or no retinopathy at the posterior pole and no abnormality other than the diabetes had numerous peripheral retinal haemorrhages. Such changes were not observed in a nondiabetic control group matched for sex and age.

The early and main pathological changes in diabetic retinopathy are usually described in the posterior central portions of the eye, particularly temporal to the macula.[1 2] Light microscopic examinations of trypsin digest preparations of specimens showing advanced retinopathy confirm this. But little information has been published on changes in the far periphery of the diabetic fundus.

Norton and Gutmann[3] and Davis[1] have drawn attention to the unique value of biomicroscopic examination of the retina in association with the study of fluorescein pictures for assessing early diabetic retinal lesions. We noted small haemorrhages in the periphery of the retina next to the ora serrata in cases of juvenile-onset insulin-dependent diabetes mellitus of long duration with minimal or no signs of diabetic retinopathy at the posterior pole. To assess if this was more than a chance observation these patients were compared with a matched control group of nondiabetic patients.

Subjects and methods

The experimental group of diabetic patients consisted of 4 men and 4 women. Their ages and the duration of diabetes are shown in Table 1. All had juvenile-onset insulin-dependent diabetes and were well controlled with diet and insulin (Table 1). They received no medication other than insulin.

All 8 diabetic patients were part of a separate research project whose inclusion criteria required an insulin-dependent diabetes mellitus of more than 25 years' duration. All patients had undergone an extensive medical assessment as part of that project. This included a detailed medical history, physical examination, and numerous investigations. Carbohydrate metabolism was assessed with repeated standard blood glucose with a Beckman analyser, continuous glucose monitoring measurements by means of a continuous-flow analyser as described by Albisser *et al.*,[4] urine glucose levels, and haemoglobin A_1C assay. Fasting plasma cholesterol, triglycerides, and lipoprotein electrophoresis, and the levels of alanine and 12 different amino acids were studied. Hormonal blood level measurements included catecholamines, free insulin, C peptide, glucagon, human growth hormone, somatostatin, pancreatic polypeptide, gastric inhibitory polypeptide, and cortisol. In the fasting patient human growth hormone, glucagon, and C peptide levels were also measured after arginine infusion. Urinary C peptide excretion was measured. The presence and severity of diabetic complications were assessed quantitatively by measurement of nerve conduction velocities and kidney function. Platelet function, status of coagulation, and the fibrinolytic system were studied extensively in all patients.

The ophthalmological assessment included corrected visual acuity, measurement of intraocular pressure and central retinal artery diastolic pressures, and examination of the ocular media. Particular attention was given to the biomicroscopic examination of the fundus with the Goldmann

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Table 1 *Age, duration of diabetes (years), and insulin requirements (number of units morning/evening)*

Diabetics								*Controls*
				Insulin				
Sex	*No.*	*Age*	*Duration*	*Regular*	*NPH*	*Lente*	*PZI*	*Age*
M	1	49	47	11/0		12/10		44
	2	39	26	10/0			40/0	36
	3	49	33	15/10/10		0/15		54
	4	66	53	12/5		12/0		63
F	5	44	36	8/0		10/4		43
	6	48	39	6/0		22/0		47
	7	37½	30	6/0		22/0		32
	8	40	32	14/0	18/0			42

3-mirror contact lens. The retinal lesions were drawn on a fundus chart and correlated with the findings of fundus photographs and of fluorescein angiography performed on all patients. Visual fields were assessed with the Amsler grid and the Goldmann perimeter. Colour vision was tested with the Farnsworth 100-hue test.

The diabetic patients were matched for sex and age (within 5 years) with a nondiabetic control group of patients attending the regular refraction clinics. None of these control patients had a systemic or ocular disorder or received any medication. They had a complete ophthalmic examination, including biomicroscopy of the retina with the Goldmann 3-mirror contact lens, with a search for small peripheral lesions.

Results

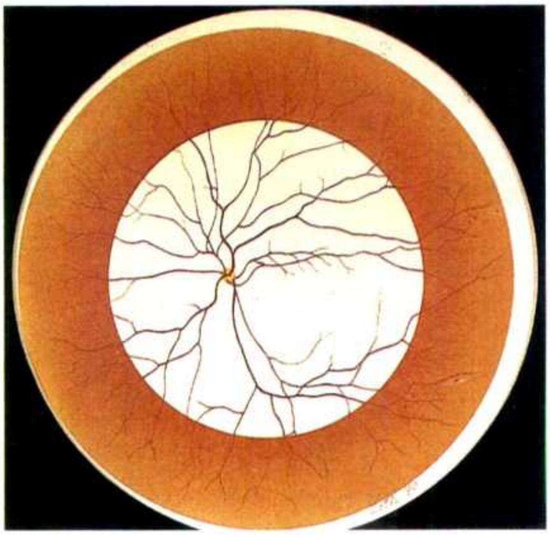
General medical studies showed that all the diabetic patients had well controlled diabetes with only occasional hypoglycaemic episodes. The patients had no clinical signs of peripheral vascular disease. There were no bruits over the carotid arteries. The systemic and diastolic blood pressures were normal in all patients. Patients 3, 4, and 5 had evidence of a mild peripheral neuropathy on clinical and nerve conduction tests. There were no abnormalities of coagulation or in lipid or hormonal assays. Patients 1, 2, 3, 4, and 5 had undetectable urinary levels of C peptide (normal value 36 μg/day). Patients 6, 7, and 8 had urinary C peptide levels ranging from 1·96 to 6·61 μg/day—still well below normal levels.

The general ophthalmic examination was noncontributory (Table 2). In patient 4 visual acuity was decreased to 20/40 and 20/50; this was related to nuclear opacities of the crystalline lenses. Patient 6 had some bilateral cortical lens opacities. However, in both patients the fundi were well seen. Patient 3

Table 2 *Ophthalmic examination*

	Male				*Female*			
No.	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*
Visual acuity OU	20/20	20/20	20/20	20/40/20/50	20/20	20/20	20/20	20/20
Intraocular pressure OD/OS (mmHg)	14/15	13/14	11/13	11/11	15/15	14/15	16/17	11/12
Lens	N	N	N	Nuclear opacity	N	Cortical opacity	N	N
Iris	N	N	depigmentation	N	N	N	N	N
Vitreous	N	N	N	?	N	N	N	N
Amsler	N	N	N	N	N	N	N	N
Perimetry	N	N	N	Contraction	N	N	N	N
Farnsworth 100-hue OD/OS	248/298	174/216	394/229	108/45	44/27	50/48	57/23	107/57
Retinopathy OD/OS:								
Microaneurysms	–/≤5	≤10/≤10	≤10/≤5	–	–/≤5	–/≤5	–/≤5	≤5/–
Haemorrhages:								
central	–	–	≤5/≤5	≤5/≤5	–	–	–	≤5/–
peripheral	≤10/≤10	≤10/≤10	≤10/≤10	≤5/≤5	≤10/≤5	≤10/≤10	≤5/≤10	≤10/≤20
Central retinal artery diastolic pressure OD/OS (mmHg)	45/50	35/36	35/36	40/42	37/37	36/37	42/45	35/35

N = no abnormality.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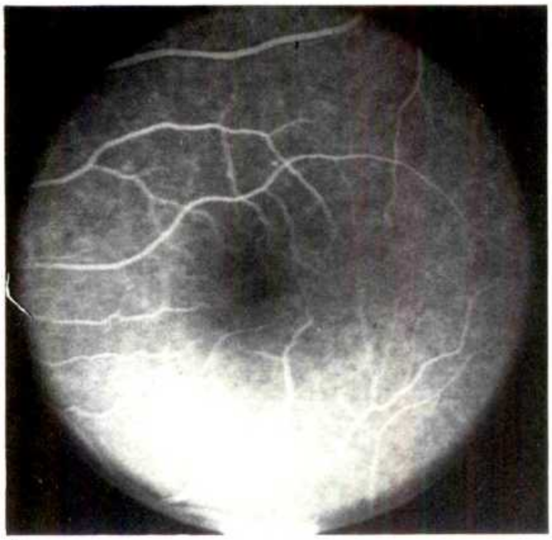
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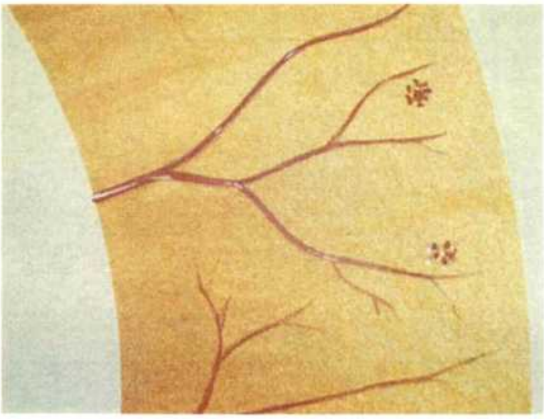
Fig. 1 *Patient 1, OS.* (a) *Drawing of minute peripheral retinal haemorrhages at 12, 2.30, and 4 o'clock.* (b) *Fluorescein angiogram of same eye showing one microaneurysm by conventional examination.*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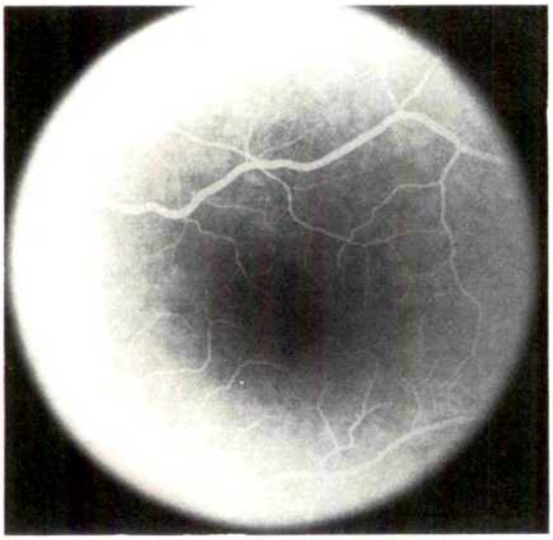
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Fig. 2 *Patient 6, OS.* (a) *Drawing of minute peripheral clustered retinal haemorrhages at 3 o'clock.* (b) *Fluorescein angiogram of same eye showing one microaneurysm by conventional examination.*

had bilateral diabetic pigmentary epitheliopathy of the iris. There was no evidence of posterior vitreous detachment or abnormal peripheral vitreoretinal adhesions. The state of the vitreous, however, was difficult to assess in patient 4 because of the lens changes. Patients 1, 2, and 3 showed high scores on Farnsworth 100-hue testing; errors were diffuse without precise axis.

The fundi of the 8 diabetics showed minimal positive findings with only aneurysms and haemorrhages (Table 2). The search for peripheral haemorrhages was a separate undertaking. They were seen in all the diabetics, and in patients 1, 5, 6, 7, and 8 their presence in one eye was the only retinal abnormality. Drawings of these peripheral haemorrhages are shown for patients 1 and 6 (Figs. 1a, 2a). The only diabetic lesion at the posterior pole was one microaneurysm in the left eye of patients 1 and 6 (Figs. 1b, 2b). These haemorrhages (Figs. 1a, 2a) lay between the equator and the ora serrata, near the terminal divisions of arterioles and venules, more often near the venules. They were more frequently seen in the temporal quadrants but were found in all quadrants. Most were superficial, round, and punctiform, lying either isolated or grouped to give a granular appearance (Fig. 2a). A few were larger, oval, and of a darker hue, and a few were linear or fusiform. In this group of patients it was possible to find from 5 to 20 separate haemorrhages in the periphery of any one eye.

In none of the patients in the control group were haemorrhages seen in the periphery of the retina.

Discussion

The present finding of peripheral retinal haemorrhages with little or no retinopathy at the posterior pole has not to our knowledge been previously reported. It is rare to submit diabetic patients with no diabetic change at the posterior pole on direct ophthalmoscopy to extensive study of the periphery of the fundus. Furthermore, attention is usually directed towards the lesions at the posterior pole because of their functional consequences.

Because the extensive clinical and biological studies made in these 8 diabetics were normal, we may conclude that there were no systemic, ocular, or therapeutic causes, other than well controlled diabetes, to account for the presence of peripheral retinal haemorrhages. However, these patients are unusual in that all but one have survived more than 30 years of diabetes, and vascular complications are very mild.

Present photographic equipment did not allow reliable assessment of the fluorescein angiographic appearance of these very anterior lesions.

It is of course speculative to make generalisations from such a small group about patients with juvenile-onset diabetes. However, it may be that peripheral retinal haemorrhages represent a breakdown of the blood retinal barrier at the peripheral vascular arcade where the retinal flow is the slowest, and the thin retinal tissue makes extravasation of blood easy and readily visible.

Our findings would tend to support Kohner's suggestion that diabetic lesions 'probably start in the periphery,'[5] though it is not certain that Kohner included lesions as peripheral as the ones reported here. In the literature large areas of capillary closure in the midperiphery of the fundus have been identified in association with proliferative retinopathy.[2] Extensive acellularity of the peripheral retinal capillaries is found in retinal digest preparations from cases of advanced diabetic retinopathy. However, this may represent not a diabetic but a senile process which starts at an early age in the peripheral retinal vessels.[6–8]

Further studies are needed, particularly in diabetes of shorter duration or with other types of retinopathy, to confirm and to assess the significance of our findings and their relationship to the familiar diabetic retinopathy at the posterior pole.

We thank Dr Marliss's laboratory for measurement of the C peptide level, Madeline Ahad for careful typing, Sandy Singer for the photographs, and Heinz Loth for the fundus drawings.

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British Journal of Ophthalmology, 1982, **66**, 290–291

Ocular complications of systemic steroid after renal transplantation and their association with HLA

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SUMMARY The eyes of 62 patients who had received allogenic renal transplants were examined for eye disease. Thirty-six patients were found to have steroid induced cataract. Six patients had ocular hypertension. Twelve patients showed arteriosclerotic changes in their fundi relating to their previous hypertension. There was no significant difference in HLA type in patients who developed cataract and those who did not. 83·3% of the 6 patients with ocular hypertension had HLA B12 in common. None of the patients had cytomegalic retinitis.

Posterior subcapsular cataract as a complication of systemic steroid has been described in the past.[1-8] Most of the studies have been done on the patients with rheumatoid arthritis, and most of them were in the older age groups. Hardly any studies have been done on younger patients. In this series of younger patients ocular complications have been assessed and their association with particular HLA antigen has been studied.

Materials and method

This series of 62 patients includes 35 males and 27 females. Their ages varied between 25 years and 60 years, mean 36 years. All the patients had chronic renal failure and had been receiving treatment with regular haemodialysis for a variable period of time between 3 months and 5½ years before renal transplantation. All the patients had received prednisolone and azathioprine. The steroid regimen was as follows: 150 mg daily immediately after the transplant, reducing by 50 mg every 3 days to a maintenance dose of 50 mg per day, and reducing weekly by 5 mg per day to 20 mg per day and 1 mg monthly to 10 mg per day. Patients with rejection episodes received up to 12 G methylprednisolone intravenously. Any patient with local ocular inflammation was excluded from the series. The haemoglobin, serum calcium, and serum phosphate levels were measured regularly before and after the transplant. None of the patients had any atopic skin conditions or any myopathy or diabetes. HLA typing was done at the Royal Liverpool hospital. A total of 40 HLA typing sera were used to determine 15 different A locus antigen specificities and 22 different B locus specificities. Their eyes were examined in detail at St Paul's Eye Hospital after periods of time from 6 months to 5 years. Their visual acuity was recorded, examination was done with ordinary light and the slit-lamp, and fundus examination was done with direct and indirect ophthalmoscopy. Intraocular pressure was measured before and after the dilatation of pupil with phenylephrine 10%. The central and peripheral fields of vision were charted.

Results

Thirty-six patients were found to have cataracts in their eyes which started after a time varying from one year to 4 years. The cataract was posterior subcapsular in type, starting at the posterior pole. It was bilateral in 29 and unilateral in 7 cases. Most of the patients had good visual acuity, more than 6/12. In one patient bilateral cataracts matured within 3 years of transplantation and required operation.

Six patients had an intraocular pressure more than 22 mmHg on applanation tonometry. These patients were considered to have ocular hypertension. The lowest pressure in this group was at 24 mmHg in one eye of one patient, and highest at 32 mmHg one of another patient. The other 4 patients had an intraocular pressure between the above figures. No pathological cupping of the optic disc was found in this group. Their central visual field was examined in the Bjerum's screen and none showed any defect. When their histocompatibility antigens were studied,

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5 out of 6 (83·5%) patients were found to have HLA B12. The incidence of B12 in patients with normal ocular pressure was 30%.

On fundus examination 5 patients showed some myopic changes. Twelve patients had reactive arteriosclerotic changes in their fundi. One patient had cystoid maculopathy and another had superior temporal vein occlusion. No other abnormality was detected in the fundi in the series.

Discussion

The high incidence of cataract following long-term steroid therapy has been reported previously. In this series out of 62 patients 36 developed cataract (58%). All had high doses of steroids after transplantation. The cataract was in the form of white dots or opacities in the posterior subcapsular region starting at the posterior pole, where the dots were more aggregated. Only in 6 eyes of 3 patients were anterior subcapsular opacities also noted. Although the patients were comparatively young, the incidence of cataract was very high in comparison with the previous report of 23% in a similar series of patients with renal transplantation.[4] Since that report immunosuppressive doses have increased, so the incidence of cataract may be dependent not only on the duration of steroid therapy but also on the dose of steroid given. An analysis was therefore done of the number of rejection episodes which necessitated an increase in steroid therapy. The results (Table 1) show no correlation between rejection episodes and incidence of cataract. An examination was also done for the length of time spent on dialysis prior to transplantation in those patients who did or did not subsequently develop cataract. No correlation was found. A comparison was made of HLA antigen distribution in those patients who developed cataract and the patients who did not. Although HLA B7 was found marginally more often in the group with cataract (16%) than in the group without cataract (14%), no definite association was suggested.

Six patients had ocular hypertension (10%), which is significantly higher than in general population. The association of HLA B12 antigen and increased intraocular pressure has been noted in the past.[5] In this group 5 out of 6 patients (83·3%) had HLA B12. The incidence of HLA B12 in patients with normal ocular pressure was 30%. Although the total number of patients with ocular hypertension is small, the presence of HLA B12 in 83·3% of them is noteworthy.

Table 1 *Analysis of rejection episodes*

	Number of patients	*Mean time on pretransplant dialysis (year) ±SD*	*Mean no. of rejection episodes ±SD*	*p (t test)*
Cataract	36	1·69±1·69	1·93±1·46	NS
No cataract	26	1·85±1·63	2·28±1·60	NS

SD=standard deviation. NS=Not significant.

Reactive arteriosclerotic changes were found in 12 patients suggestive of their previous hypertension. Acute cytomegalic retinitis as a major complication following renal transplant has been reported previously.[4] It was unusual that none of the patients in this series had suffered from this complication. It could be attributed to the improved screening of blood donors and very high doses of systemic steroids given to the patients during and immediately after the transplant.

We thank Mr R. Mapstone, consultant ophthalmologist, St Paul's Eye Hospital, Liverpool, and Dr R. M. R. Barnes, Department of Immunology, Royal Liverpool Hospital, for their help.

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British Journal of Ophthalmology, 1982, **66**, 292–302

Corneal graft rejection: a new rabbit model and cyclosporin-A

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SUMMARY In order to test the efficacy of topically applied cyclosporin-A in preventing corneal allograft rejection, existing rabbit models were modified to produce a new model in which the allograft reaction could be consistently initiated solely as a result of corneal transfer without any additional means of sensitisation. With this model, which reflects clinical corneal grafting more closely than many previous models, cyclosporin-A 1% drops applied to the recipient eye 5 times daily for 4 weeks inhibited corneal graft rejection. When cyclosporin-A 1% drops were applied to corneal allografts for 13 weeks, 44% of grafts remained clear 180 days after transplantation. No side effects were observed that could be attributed to topically applied cyclosporin-A.

Corneal grafts have been performed in animals ever since such surgery was first suggested in man.[1] Early attempts in animals to explore the feasibility of such operations produced a variety of results,[2–4] and much of the subsequent animal work was directed towards obtaining consistently clear grafts.[5–8] As materials and techniques improved, many workers achieved success rates of 75–100% in animal models,[9–13] and such work has laid the foundation for modern corneal graft surgery.

The recognition of the antigenicity of corneal tissue[14] and graft rejection in man[15] has led to the development of new animal models in order to further understanding of the allograft reaction in man. Because of the difficulty in reproducing corneal graft rejection in animals by normal methods many of these experiments relied on additional means of sensitisation of the allograft, such as delayed skin transfer[9 16] or transfer of previously sensitised lymphocytes,[17] in order to produce a consistently high rejection rate. Another method used to encourage allograft rejection has been to promote vascularisation by the use of eccentrically placed lamellar grafts or delaying suture removal in centrally placed penetrating grafts, but many such grafts fail to undergo rejection.[18] Xenografts have been found to have a consistently high rejection rate in animals,[19 20] and both allograft and xenograft models have been used to investigate methods of suppressing the immune response by means of drug therapy.[19 21–23]

Cyclosporin-A (CyA) administered by intramuscular injection has been reported to suppress the allograft reaction in a rabbit model which relied on additional skin transfer in order to sensitise the animal,[24] though when applied topically to the recipient eye in the same model it had no effect.[25] CyA, however, may have potentially serious side effects when administered systemically in man,[26] and these would limit its use in clinical corneal grafting. It also appears that CyA acts early in the immune response and to be effective should be given at the time and place of sensitisation,[26 27] which is not possible by topical application in existing models of the corneal allograft reaction.

We therefore set out to develop a new model of corneal graft rejection in which the allograft reaction is initiated solely as a result of the transplanted corneal tissue without any additional means of sensitisation. This would enable CyA to be delivered as a topical agent to a site where it may be effective. A new model is described together with the results of its use with various schedules of CyA treatment.

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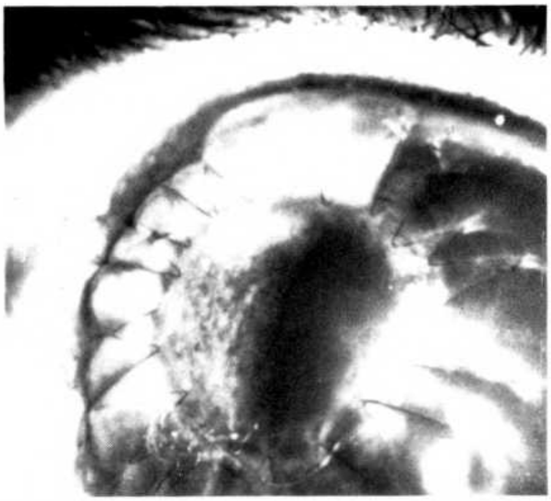


Fig. 1 *Rabbit autograft (day 4) sutured with continuous 10/0 monofilament nylon showing iris detail and dilated pupil edge through the clear graft.*

Materials and methods

Outbred strains of Dutch and New Zealand white rabbits weighing between 0·7 and 3·8 kg underwent partial penetrating corneal grafts either as pairs for allografts (one of each type of rabbit) or singly for autografts. Preoperatively, the animals were given intravenous pentobarbitone sodium (60 mg/ml) in doses varying between 0·8 and 2·5 ml according to their weight and response to the anaesthetic. Topical anaesthetic drops (proparacaine HCl 0·5%) were instilled into their right eyes together with drops of cyclopentolate 1% and phenylephrine 10% to achieve maximal dilatation of the pupil. 1 ml of heparin (5000 units/ml) was given intravenously to each animal in order to prevent clotting of the secondary aqueous. All operations were performed under an operating microscope.

OPERATIVE TECHNIQUE

After fixation of the eye by means of 4/0 silk sutures to 2 recti muscles a 6 mm trephine was used to perform a partial penetrating keratoplasty placed eccentrically in the upper temporal quadrant of the right cornea of each animal. The graft was positioned in such a way that a 1–2 mm margin of host cornea was visible at the point where the graft came nearest to the limbus. After the anterior chamber was entered with the trephine, the incision was completed with corneal scissors. The corneal discs were then interchanged and held in place initially with 4 interrupted 10/0 monofilament nylon sutures which were removed at the end of the operation. A continuous 10/0 monofilament nylon suture was then used to secure the graft with the knot placed on the side of the graft nearest the limbus in order to encourage vascularisation, with no attempt being made to bury the knot (Fig. 1). The anterior chamber was not artificially reformed; thus the iris was left in contact with part of the corneal wound to promote the formation of synechiae and subsequent deep corneal vascularisation. At the end of the procedure chloramphenicol ointment was placed on the operated eye at the same time as some animals received their first dose of CyA. Autografts were performed in an identical manner except that the discs were sutured back into the same animal.

POSTOPERATIVE MANAGEMENT

All animals received atropine 1% drops and chloramphenicol ointment daily until the removal of the corneal suture on the 14th day. On the first postoperative day slit-lamp examination was carried out and the following points were noted: the clarity of the graft and host cornea, anterior chamber depth and reaction, extent of corneal/iris adhesions, and any evidence of lens damage. Subsequent daily slit-lamp examinations were performed to assess the rate of the clearing of the graft, the progression of vascularisation, and any evidence of uveitis or allograft reaction.

CORNEAL REVASCULARISATION

In order to investigate the mechanism of graft tolerance in 6 animals whose corneal grafts had remained clear for longer than 6 months silver nitrate was applied to the corneal surface at the graft-host interface. A series of small burns were produced with a crystal of silver nitrate leaving the central graft area unaffected. The procedure was repeated after an interval of 2 days, and the animals were observed for signs of vessel reactivation and evidence of allograft rejection in the central graft area.

DIAGNOSIS OF THE ALLOGRAFT REACTION

The appearance of one or more of the following clinical signs was taken to indicate the onset of the allograft reaction[28]: (1) the clouding of a part or all of the corneal stroma in a graft which had previously been clear; (2) epithelial rejection line; (3) endothelial rejection line.

Graft survival was then recorded in days from the date of surgery until the first day on which any of these signs appeared. Usually the progression of the allograft reaction was observed for a few days in order to confirm the diagnosis before the animal was killed. The whole eye was then removed and placed in 10% formal saline.

HISTOLOGICAL METHODS

After fixation the globes were opened either parallel to the antero-posterior axis to provide sections of the whole eye, or, more usually, the anterior segment alone was processed. Sections of paraffin-embedded material cut so as to include the limbal and central margins of the eccentrically located graft were stained with haematoxylin and eosin and by the periodic acid-Schiff sequence. In 2 instances in which punctate opacities were observed in the donor cornea frozen sections were prepared for the demonstration of lipid by means of oil red 0 and Sudan black stains.

CYCLOSPORIN-A

A number of rabbits in the study were treated on a coded basis with either intramuscular CyA for 2 weeks (18 rabbits) or CyA 1% in arachis oil applied topically to the recipient eye 5 times daily for an initial period of 4 weeks (30 rabbits). In the intramuscularly treated group 8 rabbits received a dosage of 25 mg/kg for 2 weeks, as this dose had been used in previous studies.[22,23] This was later reduced to 15 mg/kg in the remainder of the group in an attempt to minimise side effects. In the topically treated group 9 rabbits continued treatment for a total of 13 weeks, but on a reducing dosage (twice daily for 5 weeks then once daily for 4 weeks). Out of the control group (33 rabbits) 14 rabbits received topical arachis oil drops 5 times daily, thus acting as a simultaneous control group for those animals receiving topical CyA in a fully coded trial.

EXCLUSION FROM RESULTS

Nineteen out of 88 rabbits were excluded from the analysis of results because of complications in the immediate postoperative period (Table 1) and 9 rabbits because they failed to survive to a point where their grafts underwent rejection (Table 2).

Table 1 *Surgical factors leading to exclusion from results in 19 out of 88 rabbits undergoing penetrating keratoplasty*

	No. of rabbits
Flat anterior chamber	7
Endothelial damage	3
Lens damage	3
Postoperative hyphaema	2
Anaesthetic deaths	2
Infected graft	1
No iris adhesions	1

Table 2 *Late deaths occurring in 9 out of 69 rabbits undergoing penetrating keratoplasty according to type of graft and treatment*

Group (total rabbits in group)	*No. of deaths*	*% Deaths/group*
Autografts (7)	—	0
Allografts—controls (25)	1	4%
Allografts—topical CyA (24)	2	8·4%
Allografts—systemic CyA (13)	6	46·2%

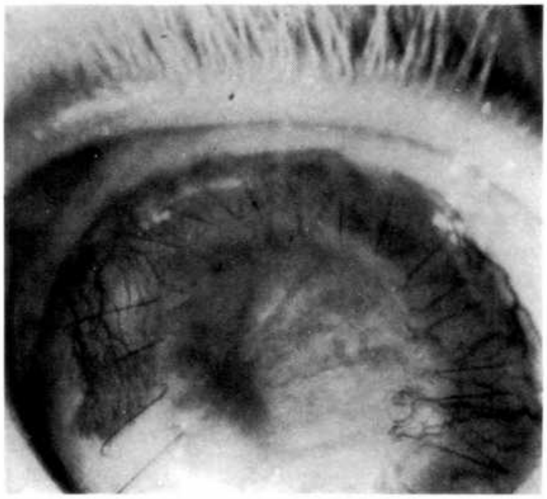


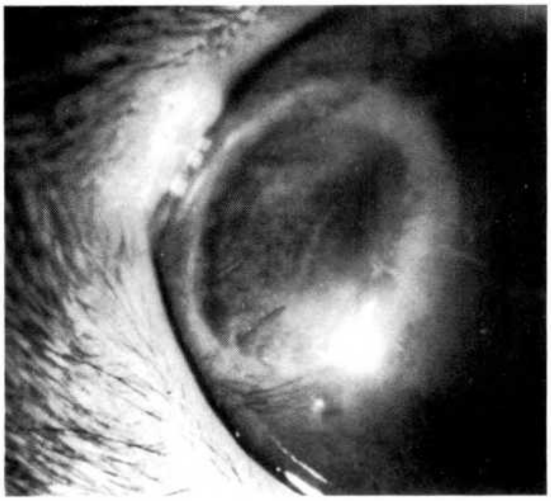
Fig. 2 *Rabbit allograft (day 14) showing a clear graft with ingrowing vessels around suture line.*

Results

All allografts in the control groups (including those that had received topical arachis oil to the recipient eye) underwent rejection. In the groups treated with CyA the onset of rejection was delayed in 24 animals and failed to occur in the remaining 5 after 180 days. The autografted group retained clear grafts for periods longer than 6 months. These results are described below.

CLINICAL COURSE

After transplantation all grafts cleared between the first and seventh day except in the part which was adjacent to the site of iris/graft adhesions. These involved between 90° and 180° of the circumference of the graft lying closest to the limbus. In addition a rim of oedema persisted along the suture line in the donor and host cornea. This oedema was thought to be related to retraction of Descemet's membrane or to endothelial trauma at the time of surgery. Superficial vessels started to grow from the limbus and reached the graft/host interface by the end of the first week, after which they progressed around and into the graft. By the time of the removal of the suture on the 14th postoperative day they usually involved three-quarters of the graft's circumference (Fig. 2). Deeper vessels arising from the iris also invaded the graft to a lesser degree.



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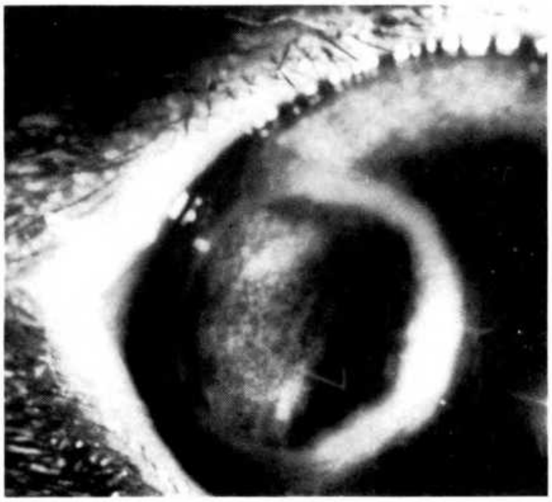

3b

Fig. 3 *Rabbit autograft (the same animal as Fig. 1) showing* (a) a clear graft with vascular ingrowth (day 18) and (b) *a clear graft with scar tissue at the graft/host interface and complete regression of vessels (day 46).*

In those animals undergoing autografts or allografts treated with CyA, after the removal of the suture vessels continued to grow around the host/graft interface where some residual oedema persisted (Fig. 3a). Then during the third and fourth weeks the vessels gradually became less active and by the fifth or sixth week were visible only as 'ghost' vessels (Fig. 3b). This complete regression of vessels was not observed in the control groups, as the rejection process supervened during this period.

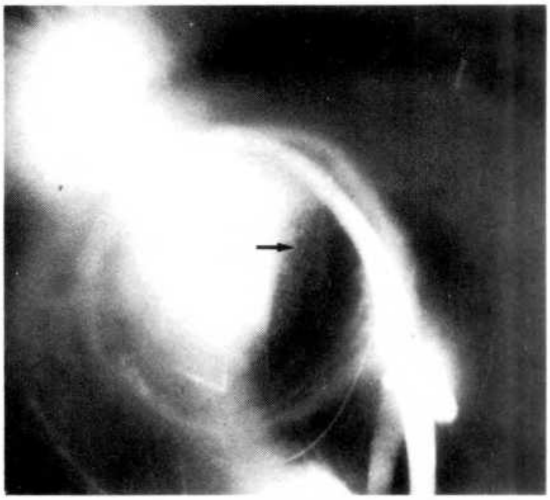

Fig. 4 *Rabbit autograft (day 44) viewed with slit illumination showing superficial stromal punctate opacities (arrowed) in an otherwise clear graft.*

A small number of rabbits developed collections of punctate opacities close to ingrowing vessels in the superficial stroma of an otherwise clear cornea. These later tended to coalesce and assume a refractile appearance, suggesting the presence of lipid. They were not thought to represent any part of the immune reaction, because they occurred in both host and graft and, in 2 cases, in autografted rabbits (Fig. 4). Histologically several small extracellular deposits of lipid were demonstrable in appropriately processed sections of the donor cornea immediately beneath the epithelium (Fig. 5). There was no sign of leucocytic infiltration, and the lipid was presumed to have originated from the adjacent intracorneal blood vessels.

The histology of all the autografted corneas showed healing, with negligible scar tissue formation and no retrocorneal fibrosis. Corneo-irideal adhesions were apparent in 5 of the animals, with some residual vascularisation in one, but there was no leucocytic infiltration, and the donor epithelium, stroma, and endothelium appeared healthy in every instance. There was therefore no evidence of rejection in any of the autografted animals.

ALLOGRAFT REACTION

All 3 clinical features by which the allografts reaction may be recognised in corneal grafts[28] were observed in each group of allografts (Table 3). The process of rejection seen in this series of allografts appeared to correspond almost exactly with previous descriptions of the allograft reaction in various corneal layers.[28]

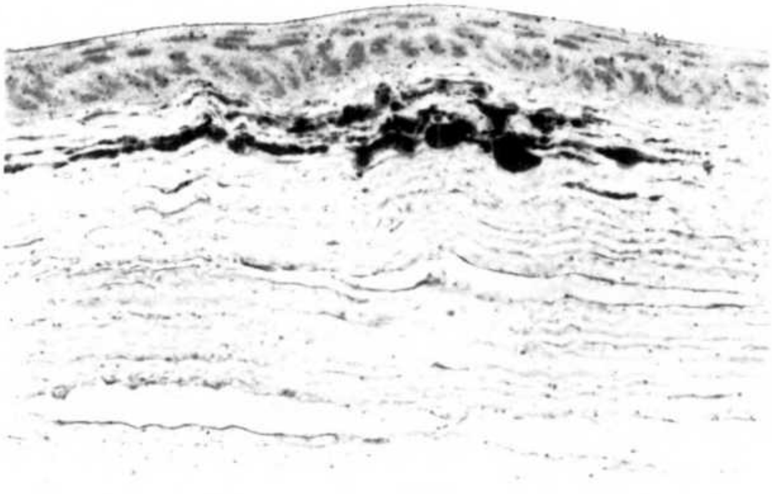

Fig. 5 *Rabbit autograft. Immediately deep to the epithelium in the grafted cornea there are small extracellular deposits of lipid. (Frozen section: oil red 0 and haematoxylin. ×385).*

Table 3 *Types of corneal graft rejection seen in 60 rabbits undergoing penetrating keratoplasty*

Group	*Rejection*			*No rejection*
	Graft oedema	*Endothelial rejection*	*Epithelial rejection*	
Autograft	—	—	—	7
Allograft (Control)	13	2	9	—
Allograft (Top.CyA)	4	6	7	5
Allograft (Syst.CyA)	1	3	2	1
Total	18	11	18	13

Graft rejection always started near invading blood vessels, usually at the site of maximal vascularisation, and progressed into previously clear cornea. In any one corneal layer the rejection process was usually established in the whole graft within 7 days of its onset, although in those animals treated with CyA the process took up to 14 days. Epithelial rejection lines could progress rapidly across the graft (Fig. 6) with only minimal disturbance in the anterior stromal layers, but this was then followed about one week later by the appearance of stromal or endothelial rejection (Fig. 7). Where the reaction was confined to the epithelium and anterior stroma, no evidence of

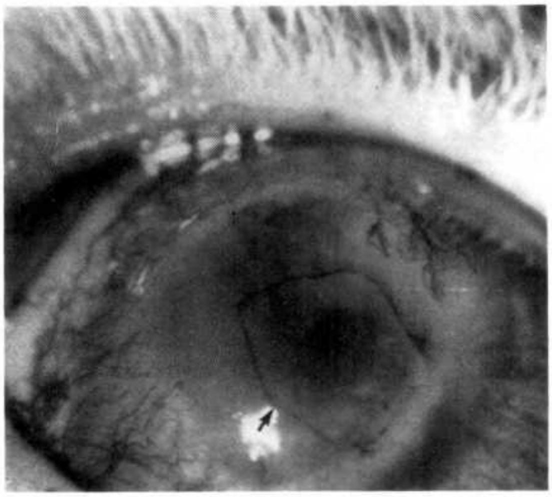

Fig. 6 *Rabbit allograft (day 38) treated with topical CyA drops from day 0 to day 28 showing advancing epithelial rejection line stained with methylene blue (arrowed).*

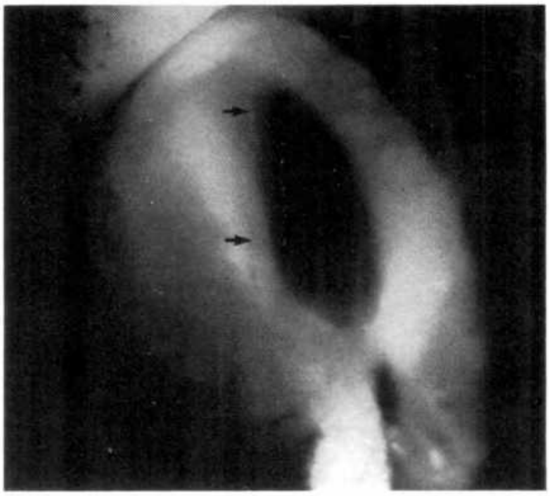

Fig. 7 *Rabbit allograft (day 81) treated with topical CyA drops from day 0 to day 91 showing endothelial rejection line (arrowed) viewed partly by retroillumination.*

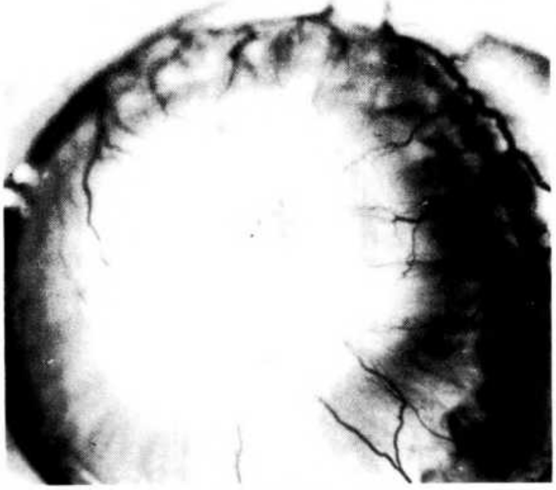

Fig. 8 *Rabbit allograft (the same untreated control animal shown in Fig. 2) showing total rejection with opacification and complete vascularisation of the graft (day 28).*

uveitis was seen. Even in those cases that developed endothelial rejection lines only a few cells were seen in the anterior chamber. Eighteen out of 60 clear grafts developed diffuse graft oedema (Fig. 8) without endothelial or epithelial rejection lines, and this appearance was subsequently confirmed as being due to the allograft reaction on histopathological grounds.

On histological examination stromal vascularisation was observed in most control animals (21 of 24 eyes) and was best seen on the limbal side of the graft, where there was cornea-irideal adhesion. Inflammatory cell infiltration, mainly in the form of lymphocytes and plasma cells with a few neutrophil polymorphonuclear leucocytes, was associated with the vascular incursions and was a feature of all specimens. Scar tissue proliferation extending from the deep surface to create limited retrocorneal fibrosis at the graft margins was observed in half the specimens. Attenuation and loss of the endothelium of variable extent with attendant stromal swelling were present in slightly more than half the specimens (Fig. 9). Keratic precipates consisting of mononuclear cells were seen in most corneas showing endothelial damage. Epithelial atrophy was apparent in the grafted corneas of most animals. All grafts in the untreated control group showed signs of immunological rejection.

All grafts in the control group underwent rejection by the 34th day, with the first graft being rejected on the 8th postoperative day (Figs. 10 and 11). The mean

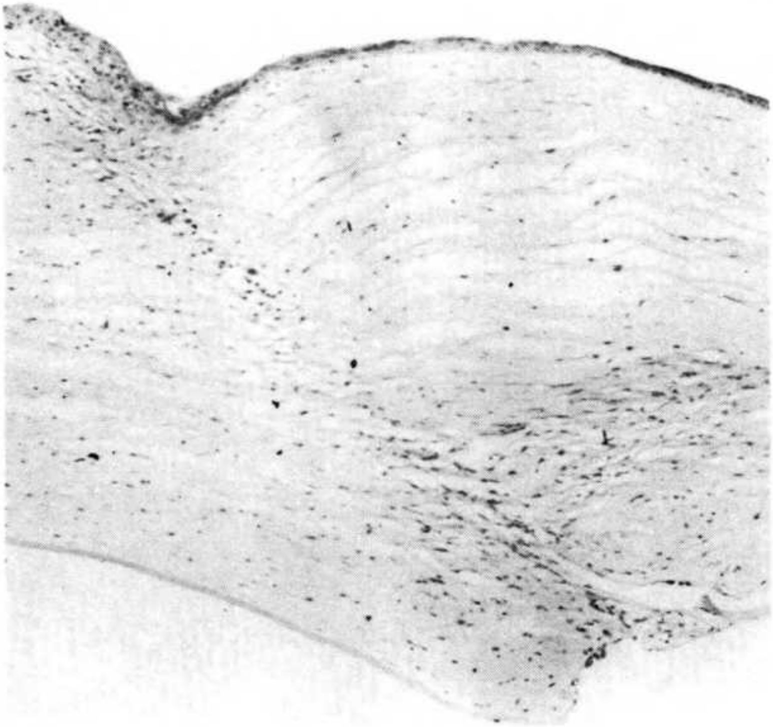

Fig. 9 *Graft-host interface displaying absence of endothelium on Descemet's membrane of the donor tissue and a little leucocytic infiltration of the graft margin. (Haematoxylin and eosin, × 107).*

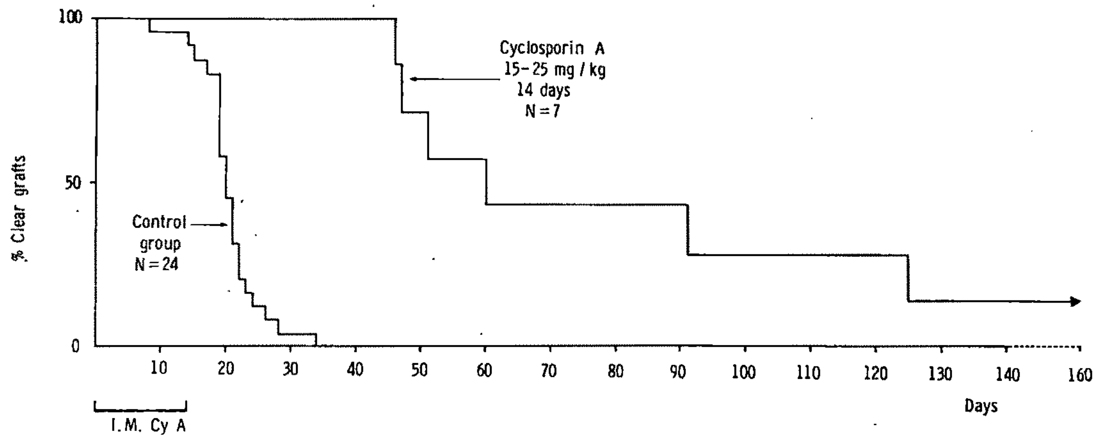

Fig. 10 *Survival of rabbit corneal allografts treated with intramuscular CyA for 14 days following transplantation.*

survival time of grafts in this group was 20·78±SD 4·80 days. The earliest rejection occurred in a New Zealand white rabbit, in which rapid vascularisation of the graft was quickly followed by the appearance of an epithelial rejection line on the eighth post-operative day. No difference was found between Dutch and New Zealand white rabbits concerning the time or rate of rejection.

CYCLOSPORIN-A

The survival rates of 3 groups of corneal allografts treated with CyA are shown in the Figs. 10 and 11.

(a) Seven rabbits treated with Intramuscular CyA (15–25 mg/kg) for 2 weeks. Six of the 7 allografts showed a prolonged period of survival with a mean survival time of 98 days compared with 20·78 days for the control group. (p<0·001). One graft in this group remained clear at 180 days (Fig. 10).

(b) Thirteen treated with topical CyA 1% in arachis oil to the recipient eye 5 times daily for 4 weeks. The first allograft in this group was rejected on day 31, 3 days after stopping treatment (Fig. 6), and the remainder had all been rejected by day 77, with a mean survival time of 47·31±12·56 days. Compared with the control group this gave a p value of <0·001 (Fig. 11).

(c) Nine rabbits treated with topical CyA 1% in arachis oil to the recipient eye for 13 weeks with a reducing dosage (5 times daily for 4 weeks, twice daily for 5 weeks, once daily for 4 weeks). Two allografts in this group developed typical endothelial rejection lines without evidence of rejection in the superficial

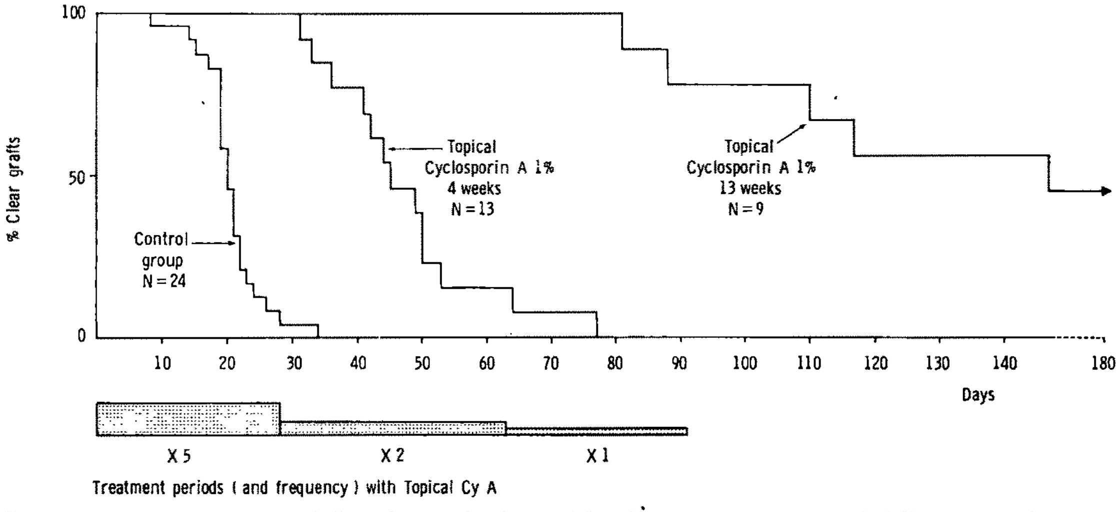

Fig. 11 *Survival of rabbit corneal allografts treated with topical CyA for either 4 weeks or 13 weeks following transplantation.*

stroma or epithelium before treatment was stopped (Fig. 7). These developed on days 81 and 88 respectively, more than 2 weeks after the treatment had been reduced from twice to once daily. Of the remaining 7 rabbits 3 rejected the grafts (days 110, 117, and 147), while the others remained clear for more than 180 days (Figs. 11 and 12).

On histological examination all animals killed after treatment with CyA for the prescribed period showed signs of rejection manifested by endothelial cell loss, stromal swelling, and reduced thickness of the epithelium. Leucocytes were conspicuous at the graft margins in virtually every case, and in most instances inflammatory cells with newly formed blood vessels had spread into the donor tissues (Fig. 13). There was no evidence of surgical failure, the graft margins being fully healed in all specimens.

EFFECT OF CORNEAL REVASCULARISATION ON GRAFT SURVIVAL

Six animals which had maintained clear corneal grafts for longer than 6 months had their corneas revascularised by means of silver nitrate. The group consisted of 1 autograft, 1 allograft treated with intramuscular CyA 15 mg/kg, and 4 allografts which had been treated with topical CyA for 13 weeks. All corneas initially developed mild central graft oedema which cleared within a few days, associated with marked vessel reactivation in the host and graft stroma.

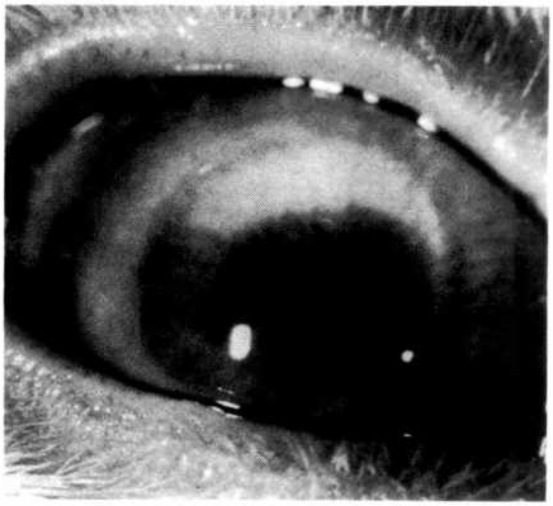

Fig. 12 *Rabbit allograft (day 150) showing a clear graft following treatment with topical CyA from day 0 to day 91.*

The autograft remained clear. The allograft which had been treated with systemic CyA developed a typical allograft reaction on the 12th day. Three out of the 4 allografts treated with CyA developed allograft reactions on the 14th, 24th, and 30th days, while the fourth developed a sustained inflammatory response lasting 5 weeks, though it later settled leaving a clear graft.

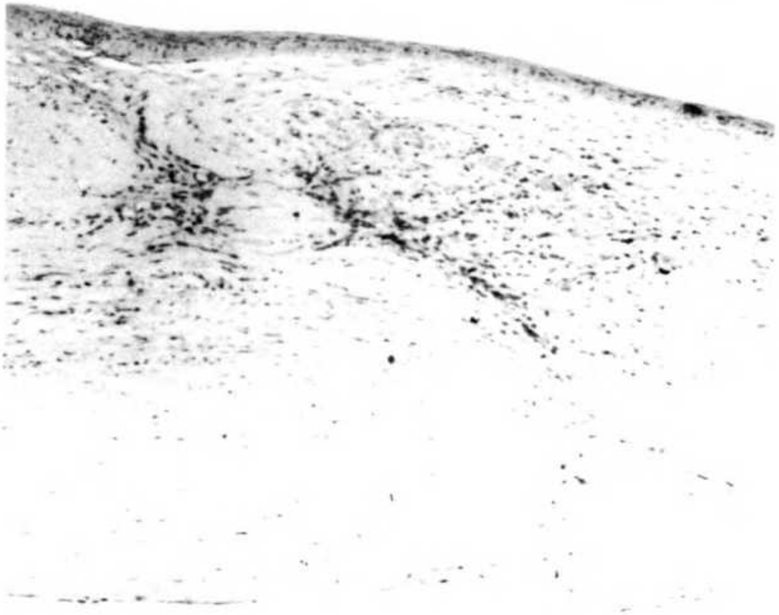

Fig. 13 *Graft-host interface showing vascularisation and leucocytic infiltration of the stroma associated with graft rejection. The donor stroma (on the left) is swollen and the donor endothelium is atrophic. (Haematoxylin and eosin, ×107).*

SIDE EFFECTS OF CYCLOSPORIN A

(a) Intramuscular CyA 15–25 mg/kg. Nine out of 11 rabbits surviving for longer than 2 weeks lost weight, and the mean weight loss for the whole group during the first 2 weeks was 0·19 kg. All other groups of animals over the same period had mean weight gains which were as follows: autografts +0·175 kg, allografts (controls) +0·22 kg, allografts (treated with topical CyA) +0·07 kg. Although this weight loss was not statistically significant, it was a notable clinical feature of the animals treated systemically during the first 2–3 weeks. After stopping CyA treatment the rabbits later regained their initial weight by about the 5th week.

In the group overall, 6 out of 13 died before their grafts were rejected (Table 2), though one was killed for reasons that could not be related to the drug. The 5 deaths (42·6%) occurred on days 14, 15, 27, 35, and 83 among animals receiving both high (2 rabbits) and low (3 rabbits) dosages. The greater death rate in this group compared with controls and topically treated groups was significant (0·05>p>0·01, *t* test).

(b) Topical CyA 1%. Two out of 24 (8·3%) rabbits died before their grafts underwent rejection, which when compared with 1 death in the control group (4%) was not significant (Table 2). One death in the topically CyA-treated group was associated with a 2-day episode of diarrhoea occurring 10 days after treatment was stopped (day 38), and the other death occurred on day 25.

All rabbits in the groups treated with either topical CyA in arachis oil or arachis oil alone lost varying amounts of fur round the treated eye (Fig. 14). This fur loss appeared after about one week and remained while treatment was continued. However, within 4–5 days of stopping treatment the fur started to regrow in all cases. Conjunctival changes were confined to mild hyperaemia of the bulbar and palpebral conjunctiva in rabbits treated with both arachis oil alone and CyA 1% in arachis oil.

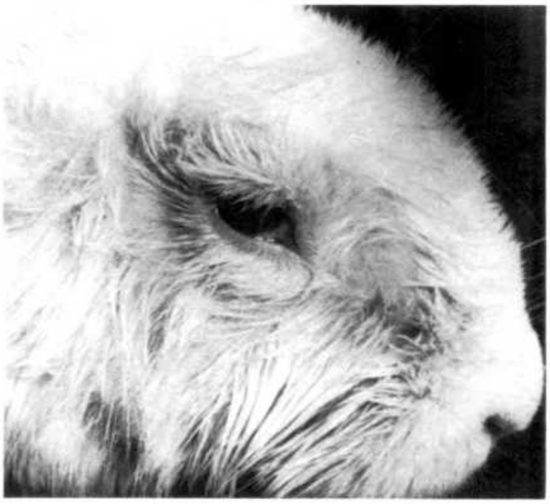
Fig. 14 *Loss of fur around eye of New Zealand white rabbit treated for 4 weeks with arachis oil drops 5 times daily for 4 weeks (day 28).*

Discussion

Although many possible mechanisms for the development of the corneal allograft reaction in man have been proposed,[29] the exact routes by which rejection may be brought about has not yet been established. Systemic mechanisms may be important in circumstances where the possibility of presensitisation by transplantation (HLA system) antigens exists, for example, from previous corneal grafts, pregnancy, or blood transfusions.[30 31] The role of the blood group antigens (ABO system), however, is less clear, and they would certainly not appear to represent a major factor in clinical corneal allograft rejection.[32 33] As a means of studying such 'second set' allograft reactions animal model utilising additional methods of sensitisation have been widely practised, yielding much valuable information.[16 17 21–25]

However, clinical corneal allograft reactions frequently occur where sensitisation would appear to have resulted only from the transfer of corneal tissue following a first graft, and to date no satisfactory 'single set' animal model has been reported. Animal models involving xenografts may induce morphological changes in lymph nodes throughout the body of a rabbit, whereas allografts in the same animal would appear to produce local lymphoid changes only.[34] There may therefore be fundamental differences between rejection of a xenograft and allograft, which makes comparison of xenograft models with clinical allografting difficult. Corneal allograft rejection by a 'single set' mechanism has been demonstrated in rabbits by means of lamellar grafts, but it was found that only 48% of grafts underwent rejection over a period of 2–6 weeks.[35] In another 'single set' model of allograft rejection involving penetrating grafts 72% of grafts took between 2 and 12 weeks to undergo rejection, leaving 28% unrejected at the end of this period.

The present model has several advantages over previous models. Firstly, 100% of untreated grafts were rejected over a period of 1–5 weeks, with a mean survival time of 20·78±SD 4·80 days. As ingrowing vessels normally take 5–7 days to reach the graft, this may indicate that the model is a more severe immunological challenge than previous systems. Secondly, rejection appears to occur as a result of a 'single set' allograft reaction, making it a closer analogue of the majority of clinical corneal graft rejections. Thirdly, it has been suggested that local immune mechanisms may be responsible for all or a substantial part of corneal allograft reactions,[29,36] and these might be altered by the local use of immunosuppressive agents. The effects of the topical use of such agents might not be observed where a model depended on additional distant sites of sensitisation. Thus, when CyA was administered topically in a 'second set' model in which it was known to be effective systemically, it failed to prevent graft rejection,[25] yet when applied topically to the grafted eye in our 'single set' model it was able to inhibit rejection.

The ability of CyA to inhibit graft rejection when applied topically to the recipient eye for 4 weeks has already been reported, and these results have been discussed elsewhere.[36] In the present experiments graft survival was further prolonged by continuing the drug for a period of 13 weeks, though the fact that 2 grafts underwent rejection while still on therapy may suggest that the treatment frequency was reduced prematurely. Even so, 44% of grafts remained clear for periods of over 3 months after treatment was stopped. It is possible that specific immunological tolerance may be induced by CyA, as has been suggested by work in other organ transplantation models.[37] However, in this model, when the experiment was carried out to produce reactivation of the corneal blood vessels, 4 out of 5 allografts rapidly developed typical corneal rejection in spite of previous treatment with CyA. It would therefore appear that the most important factor in producing graft tolerance in this model was the regression of the corneal vessels while CyA treatment was maintained, during which time the relative immunological privilege of the cornea was restored.

No side effects that could be attributed to topical CyA were found. The previously reported[25,38] transient loss of fur that occurred round the eyes of treated rabbits was found to be due to irritation by the arachis oil and subsequent scratching by the rabbit. By contrast with the rabbits treated with systemic CyA, which showed weight loss and a significantly increased death rate, the results to date indicate that topical CyA appears to be a safe drug, though this needs to be fully established by further detailed investigation.

It is hoped that the ability of topically applied CyA to inhibit corneal allograft rejection in a single-set rabbit model will enable clinical trials to begin shortly.

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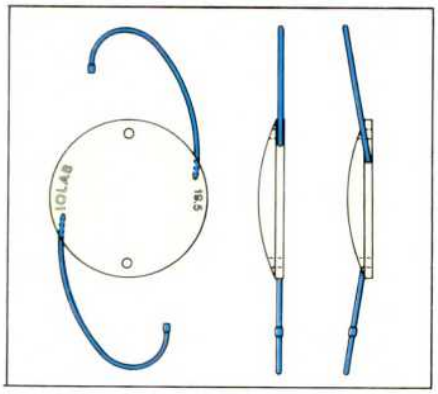

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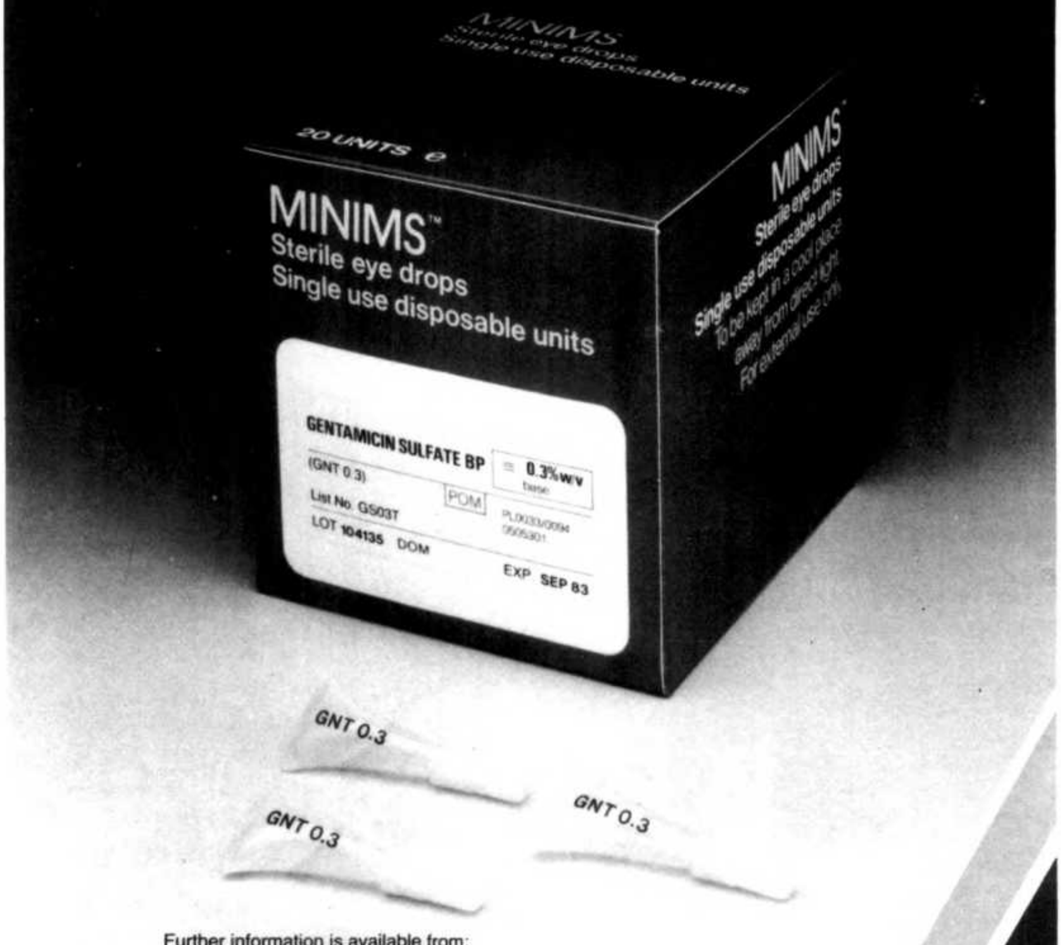

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A placebo-controlled blind trial of cyclosporin-A in prevention of corneal graft rejection in rabbits

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From the [1]Bristol Eye Hospital and [2]Searle Research and Development

SUMMARY Cyclosporin-A (CyA) administered to rabbits intramuscularly in a dose of 25 mg/kg/day for 14 days following interlamellar corneal grafting had a significant effect in preventing rejection of the corneal graft ($p<0{\cdot}05$), and the benefit was maintained. Rejection was attended by an initial mild inflammatory reaction and followed by a protracted intense response involving a variety of cell types, with subsequent loss of epithelium, endothelium and keratocytes, and the development of areas of stromal necrosis. CyA suppressed this rejection response.

Cyclosporin A, a cyclic polypeptide produced by a variety of fungi, has been shown to have a marked immunosuppressive action when given for short periods at the time of sensitisation in a variety of immunological experiments in rats and mice.[1] It appears that the drug impairs the early stage of antigenic sensitisation of immunocompetent lymphoid cells.[1 2] The drug has been shown to prolong survival of organ transplants in animals[3 4] and man.[5] The purpose of the present study was to determine by a placebo-controlled blind trial the effect of CyA in preventing corneal graft rejection in rabbits and to describe the rejection process following interlamellar corneal grafting and simultaneous skin grafting.

Materials and Methods

INTERLAMELLAR GRAFTING

Outbred New Zealand White rabbits (3–4 kg) were used. The technique used was based on that described by Basu and Ormsby.[6] A 5 mm penetrating donor button was placed in a half-depth pouch in the recipient cornea. This was fashioned by cutting a partial-depth corneal incision close to the superior limbus and dissecting downwards with a lamellar dissector. Stitches were not used.

SKIN GRAFTING

A 5 cm square piece of shaved abdominal skin was removed from the donor rabbit, cut into 4 squares, and each inserted into small pockets fashioned under the skin of the abdomen of the recipient rabbit. This was performed at the time of corneal grafting in order to ensure maximal rejection of the corneal graft.[6] Plastic spray was applied to the skin incisions and penicillin 100 000 units administered intramuscularly for 4 days.

TREATMENT

A heat sterilised preparation of CyA in olive oil (50 mg/ml) was prepared in 2 ml glass vials. Sterilised olive oil was prepared in the same way as a placebo. The preparations were coded and paired, and they were administered by intramuscular injection to 13 pairs of rabbits such that one of each pair received CyA 25 mg/kg/day and the other placebo.

Results

Slit-lamp examination was performed throughout the 14 days following grafting and comparisons of the observations made at 7 days and at 14 days. Thereafter 2 pairs were maintained without treatment for a further 8 weeks. Histological examination of corneal tissue was performed at 2 weeks and at 10 weeks.

In both groups during the first 7 days blood vessels grew into the region of the incision, and inflammatory cells were apparent in the recipient stroma. The vessels were more apparent in untreated rabbits. At 7 days 2 of the untreated rabbits had developed marked vascularisation and oedema of the recipient stroma (Table 1). Small opacities between the donor button and recipient cornea were present in both groups.

At *14 days* (Table 1) 9 untreated rabbits showed marked rejection with opacification and vascularisa-

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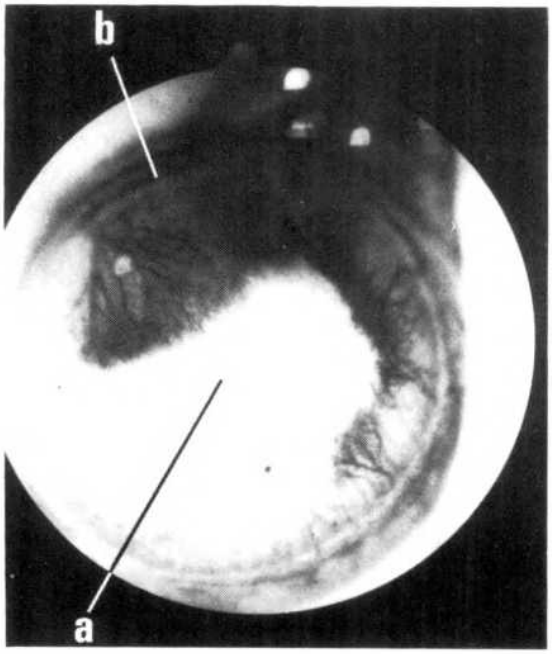

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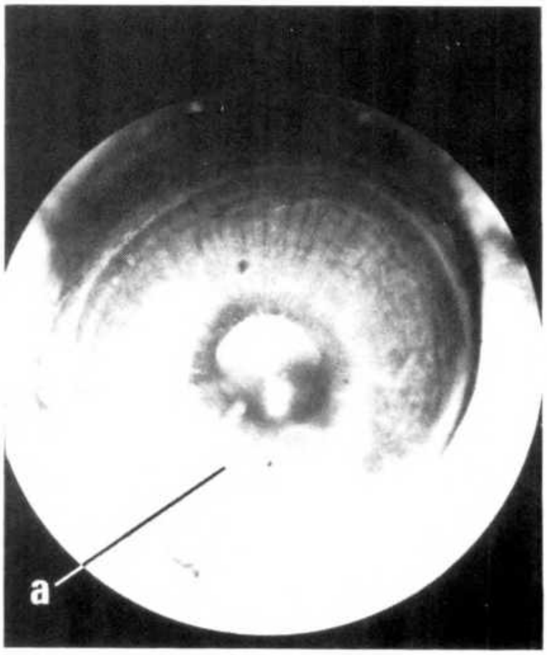

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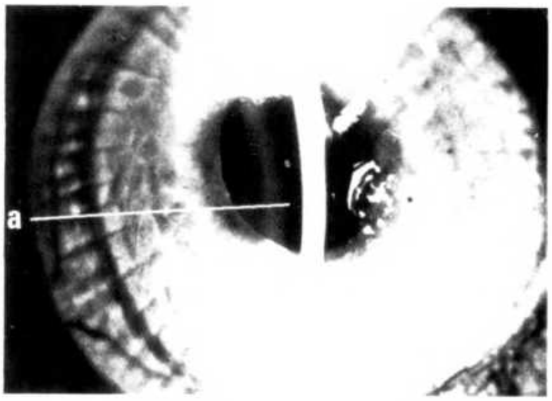

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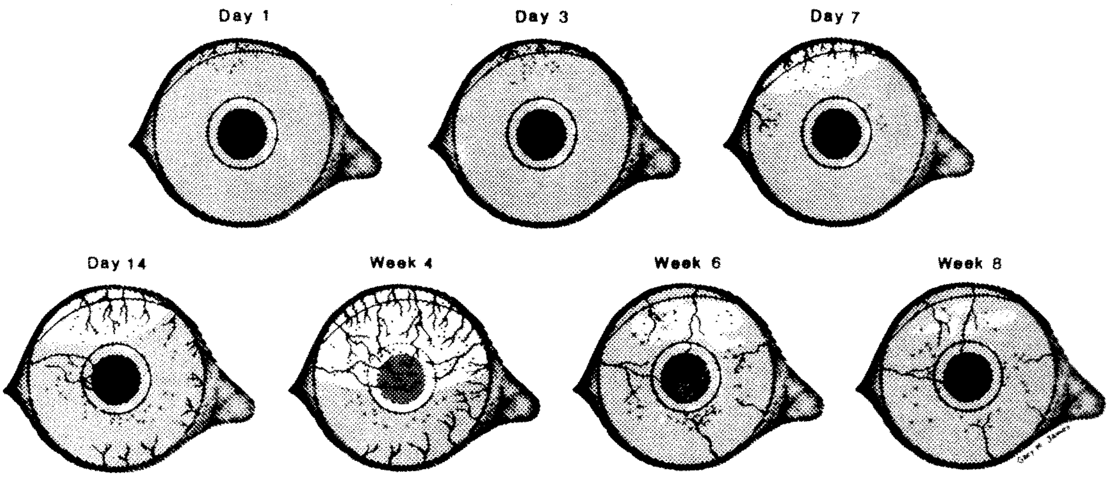
Fig. 1 *Rabbit cornea. (a) Untreated rabbit at 25 days showing intense vascularisation and oedema extending into central donor button* (a). *Incision* (b). *(b) CvA treated rabbit at 25 days showing clear recipient cornea and donor button. Interspace opacities outline the margin of donor tissue* (a). *(c) CvA treated rabbit at 10 weeks. The donor button has become incorporated and remains clear* (a).

tion of the proximal recipient stroma. Eleven treated animals showed no clinical evidence of rejection, and the corneae were completely free of vessels and opacification.

At *4 weeks* the rejection process in the untreated rabbits was maximal (Fig. 1a), while at *6 weeks* resolution was noted with reduction in oedema, vascularisation, and the appearance of macrophages infiltrating the recipient stroma and graft button. Treated rabbits (Fig. 1b) remained free of inflammation: at *6 weeks* macrophages were again noted.

At *10 weeks* (Fig. 1c) in untreated rabbits the proximal recipient stroma was no longer oedematous but was diffusely opaque. Within the deep stroma of the graft button opacities were noted. At the same stage in treated rabbits the graft edges were indistinct following incorporation of the graft into the recipient tissue. Fig. 2 shows the sequence of events in (a) untreated and (b) treated rabbits.

Opacification and vascularisation of the recipient stroma, opacification of the graft button, and limbal injection were regarded as potential criteria of graft rejection and were graded according to severity in treated and untreated animals. Stromal opacification



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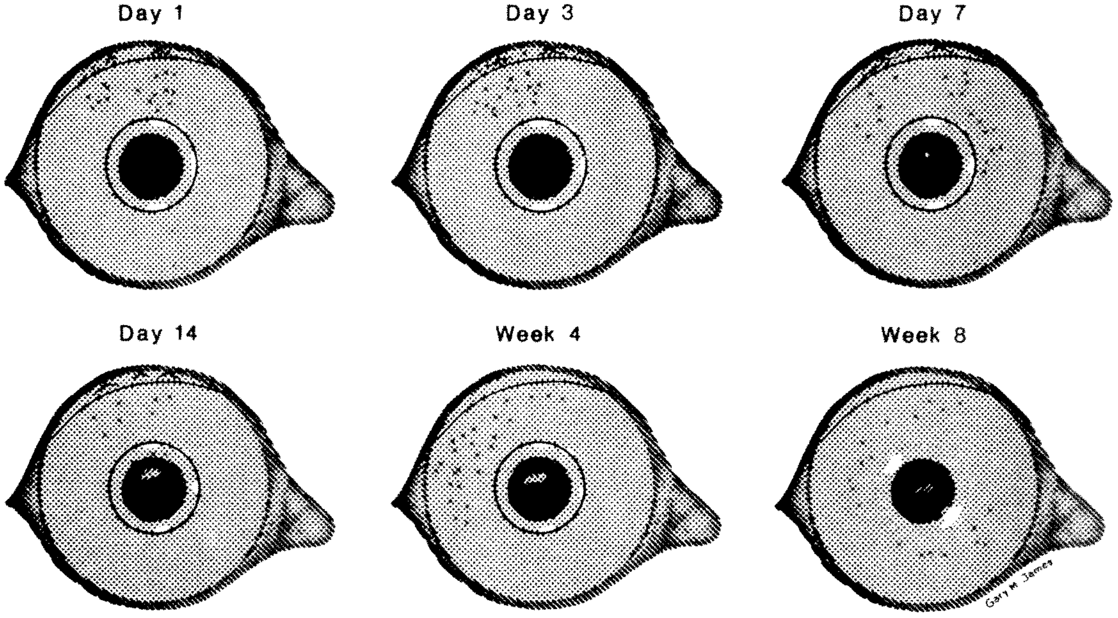


2b

Fig. 2 *Sequence of events following interlamellar corneal grafting and skin grafting. (a) Untreated: Vessels and cells develop in the region of the incision and small interspace opacities (white) develop at the graft edge. The vessels and cells increase coincidentally with oedema of the proximal recipient stroma involving the graft tissue. Resolution occurs with the appearance of macrophages in the recipient stroma and graft. Opacities (hatched) are noted deep in the graft, and the recipient stroma is slightly opacified (white). (b) Treated: Vessels and cells develop in the region of the incision and cells reach the donor tissue. The vessels and cells regress. Interspace opacities (white) appear centrally. Macrophages appear in the recipient stroma and graft and the graft edges become indistinct.*

Table 1 *Rejection response in treated and untreated rabbits at 7 days and 14 days*

		Marked rejection	*Equivocal rejection*	*No rejection*
Day 7				
6 pairs examined	Treated	0	4	2
	Untreated	2	4	0
Day 14				
13 pairs examined	Treated	1	1	11
	Untreated	9	1	2

Table 2 *Grading of opacification in recipient stroma*

Appearance	*Grade*
Absolutely clear	0
Diffuse opacification on slit-lamp examination ± small occasional opacities	1
Diffuse opacification just visible to naked eye ± occasional dense opacities	2
Diffuse opacification easily seen by naked eye ± small dense occasional opacities	3
Diffuse dense opacification	4

Table 3 *Score ranges whereby rabbits were allocated into high and low rejection groups*

Rejection criteria	*Value decided as low rejection*	*Value decided as high rejection*
Stromal opacification	0–2	3–4
Stromal vascularisation	0–1	2–3
Graft opacities	0–1	2–3
Limbal injection	0–1	2–3
Total scores	0–4	5–14

was graded as shown in Table 2. Stromal vascularisation, opacification of the graft button, and limbal injection was graded according to a simple 0–3 scale which corresponded to absent, mild, moderate, and intense responses.

At 2 weeks each rabbit was examined and a score decided for each criterion. The total score for each rabbit was also obtained. Rabbits were divided according to their score into either a group displaying absent/mild rejection or a group displaying moderate/marked rejection for each criterion and total score (Table 3). The code was then broken, and Table 4 shows the distribution of treated and untreated rabbits within these 2 rejection groups.

Statistical analysis demonstrated a significant difference in the distribution of treated and untreated rabbits within the 2 rejection groups for stromal opacification, stromal vascularisation, and total score of rejection criteria ($p<0·05, <0·05, <0·01$ respectively by chi-square test; Table 5).

Table 4 *Distribution of treated and untreated rabbits within low and high rejection groups for each rejection criteria and total score*

Rejection criteria	*No. in low rejection group*		*No. in high rejection group*	
	Treated	*Untreated*	*Treated*	*Untreated*
Stromal opacification	11	4	2	8
Stromal vascularisation	11	3	2	9
Graft opacities	12	6	1	6
Limbal injection	10	4	2	7
Total scores	11	3	2	9

Table 5 *Probability that cyclosporin-A influenced rejection favourably*

Rejection criteria	χ^2	$p<$
Stromal opacification	4·87	0·05
Stromal vascularisation	6·74	0·01
Graft opacities	3·64	NS
Limbal injection	3·53	NS
Total score	6·74	0·01

NS = not significant.

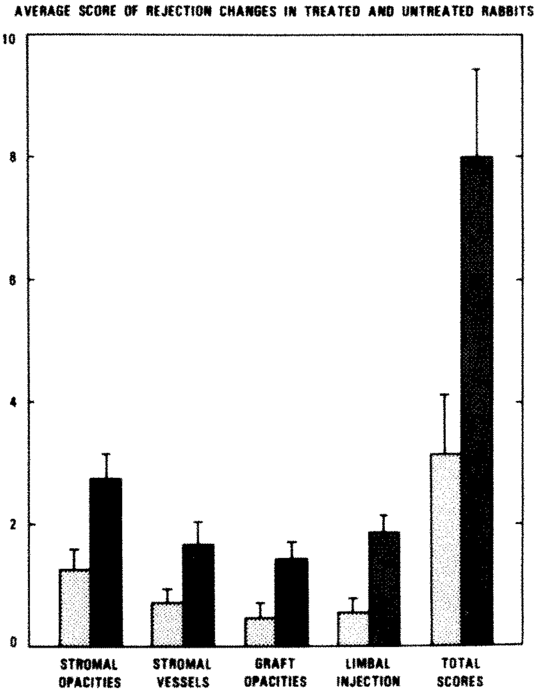
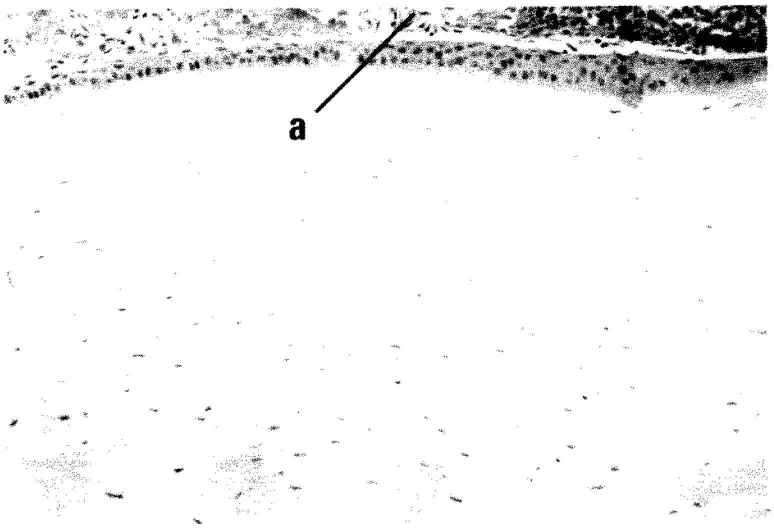


Fig. 3 *Average score of rejection criteria and total score in treated and untreated rabbits. Standard errors are shown. Dark shade: untreated rabbits. Light shade: CyA treated rabbits.*

4a



4b

Fig. 4 *Histology of donor tissue. (×260). (a) Untreated rabbit at 10 weeks. The donor tissue is devoid of keratocytes. Epithelium and endothelium are absent. (b) CvA treated rabbit at 10 weeks. Keratocytes are present and the epithelium remains healthy. Shed epithelial cells form interspace opacities* (a).

The average score for the rejection criteria in the treated and untreated rabbits are shown with standard errors (Fig. 3).

HISTOLOGY

Histological examination at 14 days in the *untreated* rabbits revealed an inflammatory reaction comprising polymorphonuclear leucocytes, lymphocytes, fibroblasts, and vascularisation in the proximal recipient stroma located in the plane of the original dissection, this reaction extending towards the graft button. The cellular infiltrate was present in the tissue both anterior and posterior to the graft button, and cells invaded the epithelium and endothelium of the donor tissue. Cells were also noted in the graft stroma in reduced numbers. A dense lymphocytic reaction was present in the ciliary body. Histological examination in the *treated* rabbits revealed no inflammatory reaction other than healing of the incision. Remnants of endothelium were present, and the epithelium was preserved.

Histological examination at 10 weeks in the *untreated* rabbits (Fig. 4a) revealed an absence of donor epithelium and a marked hypocellularity of the graft stroma with extensive areas of necrosis in the deeper layers. Vessels extended into the graft, macrophages were evident in recipient and donor tissue, and lymphocytes were noted in the ciliary body. In the *treated* rabbits (Fig. 4b) the graft was intact, with a normal population of keratocytes and an intact epithelium. Macrophages were evident in the donor button and in the recipient stroma. A macrophage and mild lymphocytic reaction was present in the ciliary body.

Discussion

The results show that CyA significantly reduced the development of stromal opacification and stromal vascularisation, which were the most obvious signs of graft rejection in this model.

Interspace opacities appeared to correspond with areas of degenerating epithelium. In untreated rabbits they were associated with inflammatory cells, while in treated rabbits they resulted from shed epithelial cells. Whereas oedema of the graft button at 2–4 weeks was a reliable indicator of rejection, the interspace opacity was not.

In this model corneal grafting is attended by the early presence of cells derived from the limbal vessels which develop in response to the incision. In the absence of CyA this cellular infiltrate is followed after an interval of several days by a marked inflammatory reaction, with intense vascularisation, increased cellular infiltration, and oedema. This protracted reaction resulted in the destruction of epithelium, endothelium, and keratocytes and would almost certainly result in failure of penetrating keratoplasty. The recipient stroma remains vascularised and opacified.

In the presence of CyA early inflammatory cells appear in the proximal stroma, but there is no subsequent inflammatory response. The observations support the suggestion that CyA impairs the early stage of antigenic sensitisation of immunocompetent cells.

The prolonged survival of the graft following withdrawal of treatment may be due to an induction of specific tolerance to the antigen by CyA as described by Green *et al.*[7] Alternatively it is possible that the corneal graft regains immune privilege after healing of the incision. It is interesting that Shepherd *et al.* were unable to induce rejection of a corneal graft in a control rabbit by sensitising 14 days later with a skin graft if the wound was not vascularised,[8] suggesting that the early inflammatory response induced in the locality of the incision constitutes a breakdown of corneal immune privilege.

Cyclosporin A has been shown to prolong survival of penetrating corneal grafts in rabbits,[8] and the present blind, placebo-controlled study supports this result. The suggested mechanism of action appears to be relevant to corneal grafting and provides a rationale for short-term use of the drug until corneal immune privilege is re-established.

CyA has been used as the immunosuppressive agent in renal transplants in man.[5] Toxic side effects including transient jaundice and changes in the liver and kidney are reported,[2] and there may be a 10% incidence of lymphoma in patients receiving the drug on a long-term basis.[2] There may be little indication for prolonged use in corneal grafting; consequently it would seem unlikely that side effects will prove to be a hazard. More information on the total dosage of CyA and the incidence of systemic complications is required before short-term use of this drug can be recommended.

We gratefully acknowledge assistance from Dr J. F. Borel of Sandoz Ltd, Professor Grunsell, Department of Veterinary Medicine, Bristol University, and Miss Clare Carter, Miss Anne McSmythurs, and Mrs Janet Williams, Pharmacy Department, Bristol Eye Hospital for assistance with preparation and coding of the materials.

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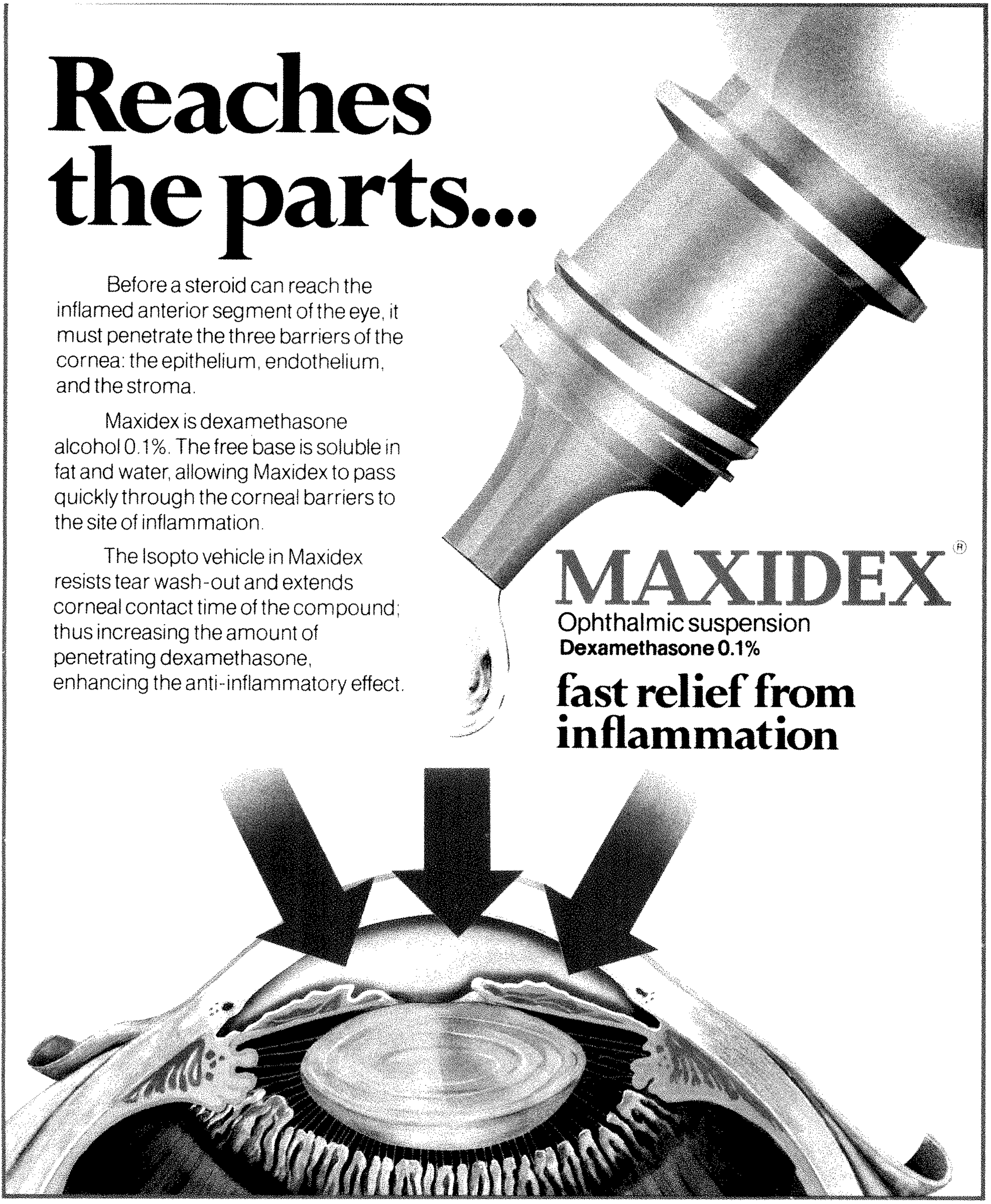

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British Journal of Ophthalmology, 1982, **66**, 309–316

Atypical band-shaped calcific keratopathy with keratocyte changes

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SUMMARY The clinical features of a patient with atypical band keratopathy are described. Histochemical and electron probe analyses indicate that the granular deposits in Bowman's layer contain calcium and phosphate. An unusual feature in this patient was the presence of severe keratocyte degeneration; its possible role in the pathogenesis of this condition is discussed. Exfoliation of the calcified Bowman's layer appears to have been the basis for severe attacks of recurrent ocular pain.

The mechanisms of ectopic corneal calcification, although the subject of much experimental work which has been reviewed by Obenberger and his coworkers,[1 2] remain largely speculative. In most patients the clinical appearance of a horizontal band-shaped opacification of the Bowman layer is associated with a variety of local and/or systemic diseases. Calcification is often referred to as 'secondary' in these cases to provide distinction from the much rarer hereditary or dystrophic variety in which no such associations are found.

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We recently observed a patient with atypical calcific opacities which gave rise to recurrent attacks of irritation and pain. Biopsy indicated that these features were associated with histological and ultrastructural changes of the keratocytes. Since some of the clinical and cytological features appear to be unique, we have compiled the following clinicopathological report.

Case history

A 41-year-old male Nigerian academic of the Yoruba tribe was first seen in January 1980. He complained of recurrent episodes of redness and photobia with

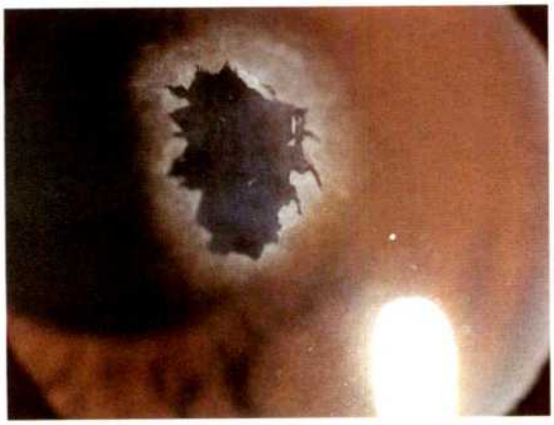

Fig. 1 *Right eye. Annular opacity in the pupillary zone of cornea. Jagged inner edge outlines central clear area.*

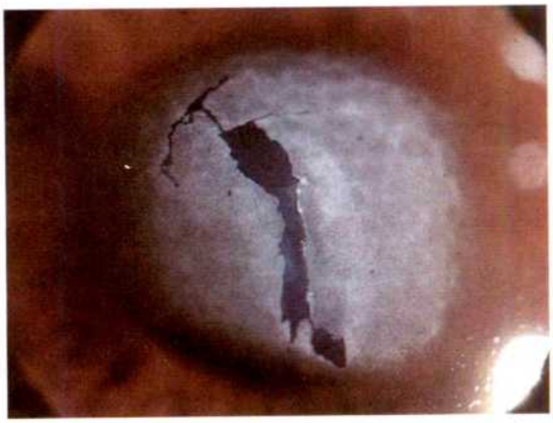

Fig. 2 *Left eye. Discoid opacity with fissures. A greyish reticulum within the opacity imparts a mosaic appearance.*

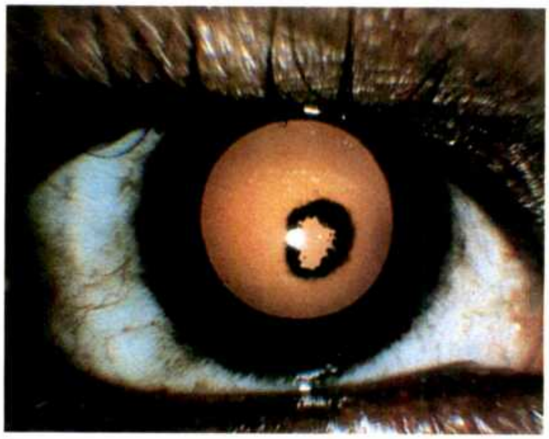

Fig. 3 *Corneal opacity in right eye is seen as black silhouette against fundus glow.*

severe pain which had affected the left eye almost weekly for the previous 4 months. Similar occurrences had affected the right eye for a period of 3½ years, but they had ceased abruptly 6 months ago. No similar eye disorder was known to have occurred in any other members of his family. The patient's health had been unremarkable until the start of these ocular symptoms. There was no history to suggest corneal exposure to chemical factors or of vitamin D intoxication.

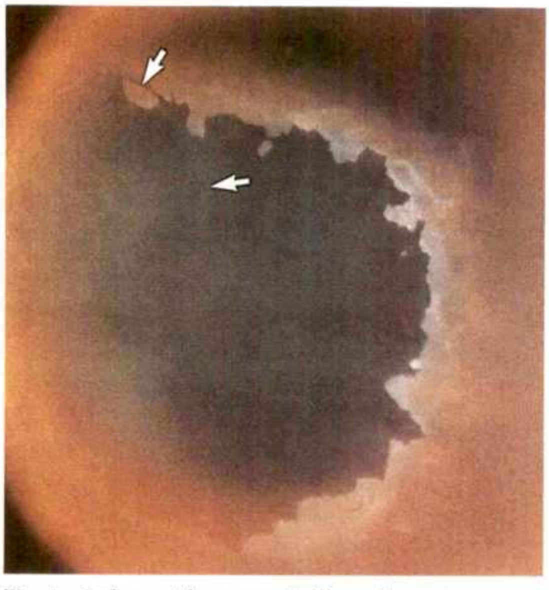

Fig. 4 *Left eye. After removal of 2 mm biopsy (arrows mark site) and debridement of most of the remainder, only a narrow rim of the original opacity remains.*

Visual acuity was 6/9, N5 in each eye when mild mixed astigmatism had been corrected. Subepithelial discoid greyish-white lesions about 3·8 mm in diameter were present in the central zone of both corneas. On the right side the lesion was annular in form, a central clear area being outlined by a jagged inner edge (Fig. 1). The left corneal opacity, which was somewhat larger, appeared as a grey disc in which white lines formed a mosaic pattern (Fig. 2). An irregular fissure running vertically almost divided the disc. The temporal edge of the fissure was slightly elevated, and the overlying epithelium stained with both fluorescein and rose Bengal. At high magnification the lesions had a granular structure. Ophthalmoscopically the opacities were silhouetted in the red fundus glow (Fig. 3). Tear and meibomian secretions and ocular tensions were normal. Sensation over the corneal opacities was slightly diminished. No other ocular abnormalities were noted.

The attacks of ocular pain affecting the left eye became more severe and incapacitating. Since it seemed likely that the quiescent state of the right cornea had been achieved by a natural exfoliation of the central part of the lesion over several years, biopsy and debridement of the left corneal lesion were undertaken under retrobulbar anaesthesia. The opaque material was removed with ease. Within 48 hours the patient was symptom-free and the left vision corrected to 6/9+. The slit-lamp appearances following this procedure (Fig. 4) now closely resembled those seen on the right side. No further attacks have occurred over the past 9 months, vision and slit-lamp appearances remaining constant.

GENERAL INVESTIGATIONS

All studies to determine the aetiology of these lesions were uninformative. Fasting levels of serum calcium, phosphate, alkaline phosphatase, glucose, and lipids were normal on 3 occasions. The Kveim test and other investigations for sarcoid were negative. There was no radiological evidence of ectopic calcification.

METHODS

A 2 mm trephine was used to biopsy the left corneal opacity. The disc, which included the anterior 1/6th of stroma, was placed in ice-cold 3% glutaraldehyde. Some of the material obtained by superficially scraping away the remainder of the opacity was fixed likewise. After dehydration the specimens were osmified and embedded in methacrylate. After staining with uranyl acetate and lead citrate, sections were examined in a Phillips 301 electron microscope. Unstained sections were subjected to elemental analysis with an Edax analysing electron probe. Orientational sections cut at 0·5 μm were stained in 1% toluidine blue for light microscopy. The

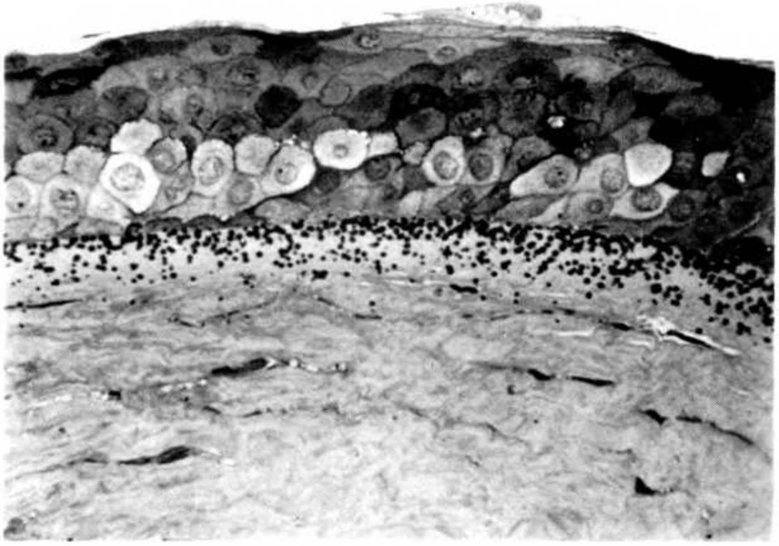

Fig. 5 *Corneal epithelium shows mild dysplasia with hydrops of some superficial squames. The Bowman layer contains intensely basophilic granules. Some of the superficial keratocytes are vacuolated. (Toluidine blue, ×580).*

remainder of the material was fixed in neutral formalin and subsequently embedded in JB4 compound (Polysciences). Sections from this material were subjected to routine histological stains, as well as certain histochemical procedures which will be indicated alongside the results obtained.

Observations. The trephined biopsy specimen and curetted material consisted of epithelium and superficial corneal stroma.

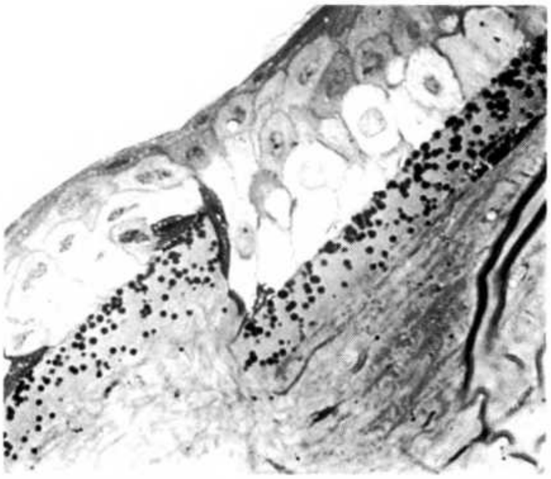

Fig. 6 *Fissure in Bowman's layer, which may be traumatic (surgical) artefact, illustrates its friability. (Toluidine blue, ×467).*

LIGHT MICROSCOPY

In toluidine blue preparations the epithelium showed mild dysplasic changes (Fig. 5). Surface squames were often swollen and vacuolated. Nests of intensely basophilic cells were seen in the intermediate layers. In many places the basal cells were separated from Bowman's layer by a stratum of vacuolated amorphous material. Elsewhere the basal cells lay directly on the Bowman layer or on the basement membrane. The Bowman layer was studded with myriads of intensely basophilic spherules, the larger of which were about 1 μm in diameter. Occasional spherules were found in the adjacent stroma. Both spherules and the basement membrane, where present, gave positive reactions with the von Kossa and alizarin red methods for phosphate and calcium respectively. The friability of Bowman's layer was indicated by occasional vertical cracks with displacement of the fragments (Fig. 6). Beneath the Bowman layer were patches of vacuolated amorphous material similar to those on its anterior surface. Throughout the stroma keratocytes showed a variety of changes which are described in infrastructural detail below.

ELECTRON MICROSCOPY

Epithelial cells which appeared dark blue in toluidine blue preparations were electron-dense and contained numerous tonofibrils. In other areas paler cells were undergoing hydropic degenerative changes, shown as cytoplasmic vesicles which were often prominently aligned under the cell membrane (Fig. 7). Similar

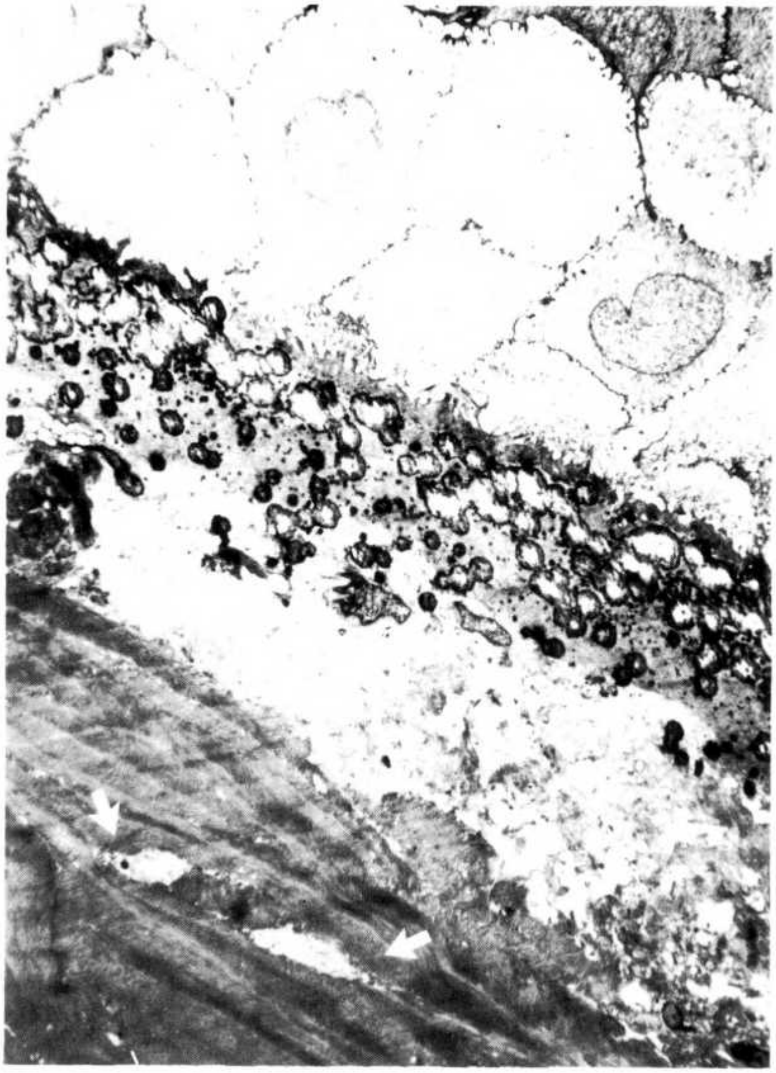

Fig. 7 *A band of amorphous granular debris is found below Bowman's layer. A degenerated keratocyte (arrows) distended with clear vacuoles is seen below. (Electron micrograph, ×1470).*

changes were seen in the basal cells. The basement membrane-hemidesmosome system was absent in some sections, the basal cells lying either directly on the Bowman's layer or more commonly on the layer of vacuolated debris, which contained a variety of fibrillar materials, including normal and 'curly' collagen (Fig. 8) as well as a variety of organelles. Similar material was also patchily distributed below Bowman's layer (Fig. 7). When the basal cells lay directly on Bowman's layer, tufts of fibrils extended upwards, producing a sawtooth appearance in the cell membrane (Fig. 7).

Bowman's layer, which was present in all sections examined, contained numerous electron-dense spherules which often showed a paler core and a denser rim, although sometimes the relative densities were reversed. The spherules consisted of tightly packed electron-dense granules which replaced or obliterated the random collagenous architecture of the Bowman's layer. Elemental analysis of the spherules by electron probe indicated that calcium and phosphorus were present in considerable quantities (Figs. 9A, B).

Degenerative changes in the keratocytes were especially severe in the vicinity of Bowman's layer; several stages of this process are suggested by their varying appearances (Figs. 10A, B, C). Firstly, the cytoplasm distends with vacuoles and electron-dense

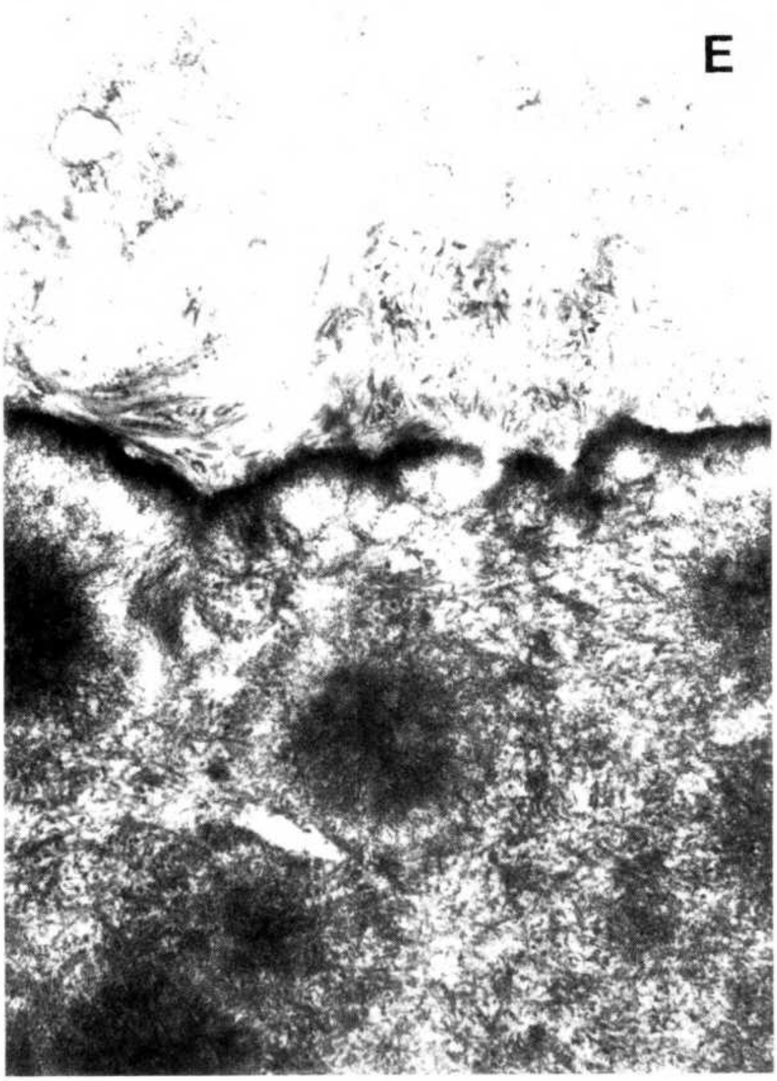

Fig. 8 *Heavily calcified portion of Bowman's layer shows concentric ring formations in some spherules. The basement membrane (also calcified) is thickened and electron-dense. A layer containing various presumed collagen fibrils separates the basement membrane from the basal epithelial cell. E. (Electron micrograph, ×32 500).*

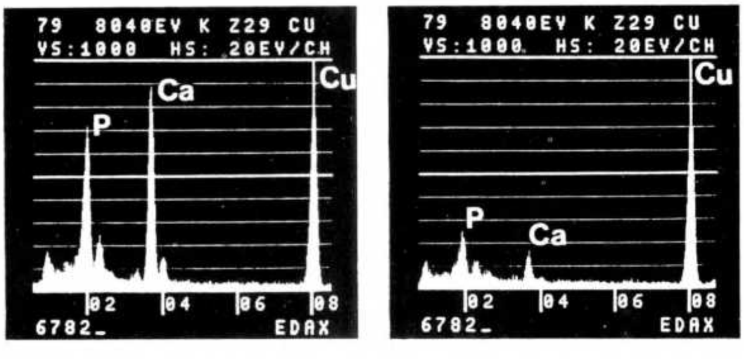

Fig. 9A *Elemental analysis of one of the spherules in Bowman's layer shows high concentration of calcium (Ca) and phosphorus (P) within the spherule, to be compared with Fig. 9B, which indicates lower concentrations of these elements in the adjacent stroma. Copper (Cu) originating from the grid holding the section is the main component in both 9A and 9B.*

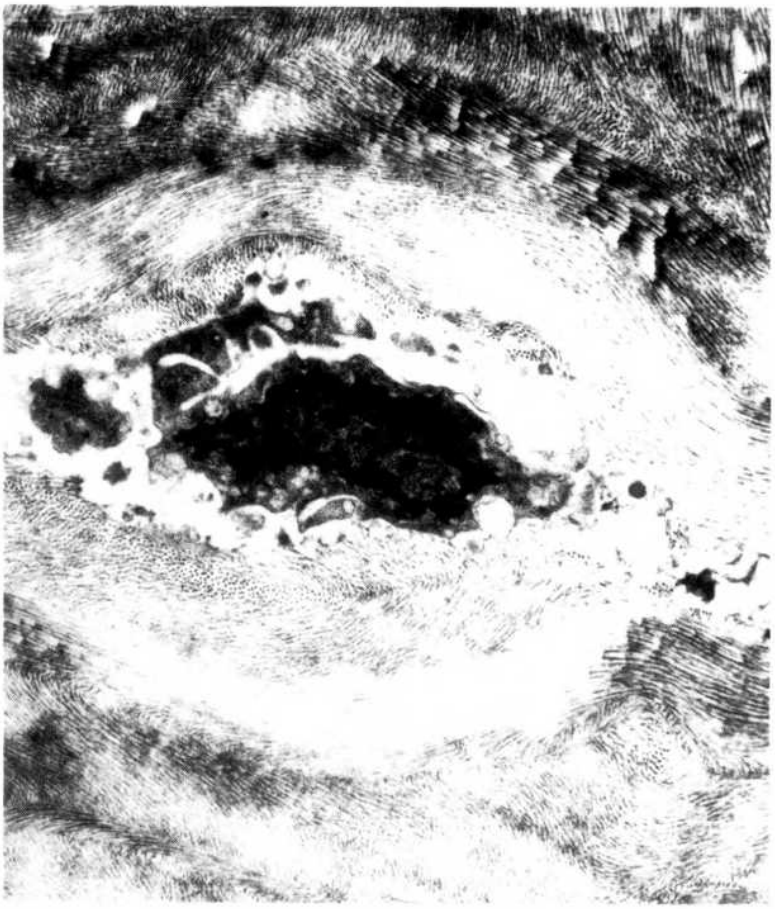

Fig. 10A *Keratocyte shows numerous vacuoles and granular inclusions. (Electron micrograph, ×14 255).*

inclusions. Secondly, the cell membrane disintegrates. Finally the cytoplasm becomes increasingly electron-lucent and occupied by degenerating organelles, the nucleus becoming pyknotic or disintegrating. Ultimately the spaces occupied by dead keratocytes become empty apart from tonofibrils and debris. 'Ghost' cells of this latter type were especially common beneath the Bowman layer. Patches of vacuolated amorphous debris below the Bowman layer were the only other abnormality in the stromal collagen.

Discussion

The corneal opacities described in this report do not appear to have been previously documented. A superficial mosaic opacity, similar to that in our patient's left eye was noted by Valerio[3] in both corneas of a young man whose father and other family members were afflicted with the primary (hereditary) form of band-shaped calcific opacity.

Histochemical and electron micro-probe elemental analysis of our biopsy material has indicated that the darkly stained spherules found in Bowman's layer contain calcium and phosphorus in considerable quantities, presumably as a calcium phosphate. An interesting finding is the presence of widespread degenerative changes in the keratocytes.

The present case should be differentiated from noncalcific band-shaped keratopathy in which subepithelial yellowish granules are the essential biomicroscopic features. Kloucek[4] studied keratectomy specimens from 2 related patients with the rare primary form of this disorder. He observed that the yellow granules corresponded with electron-dense spherules in the Bowman's layer and contained a nonlipid protein but no calcium. He also noted that keratocytes in the superficial stroma had proliferated and undergone a variety of degenerative changes, similar—if less widespread—than those seen in our patient, leading him to consider that the spherules in Bowman's layer had been produced

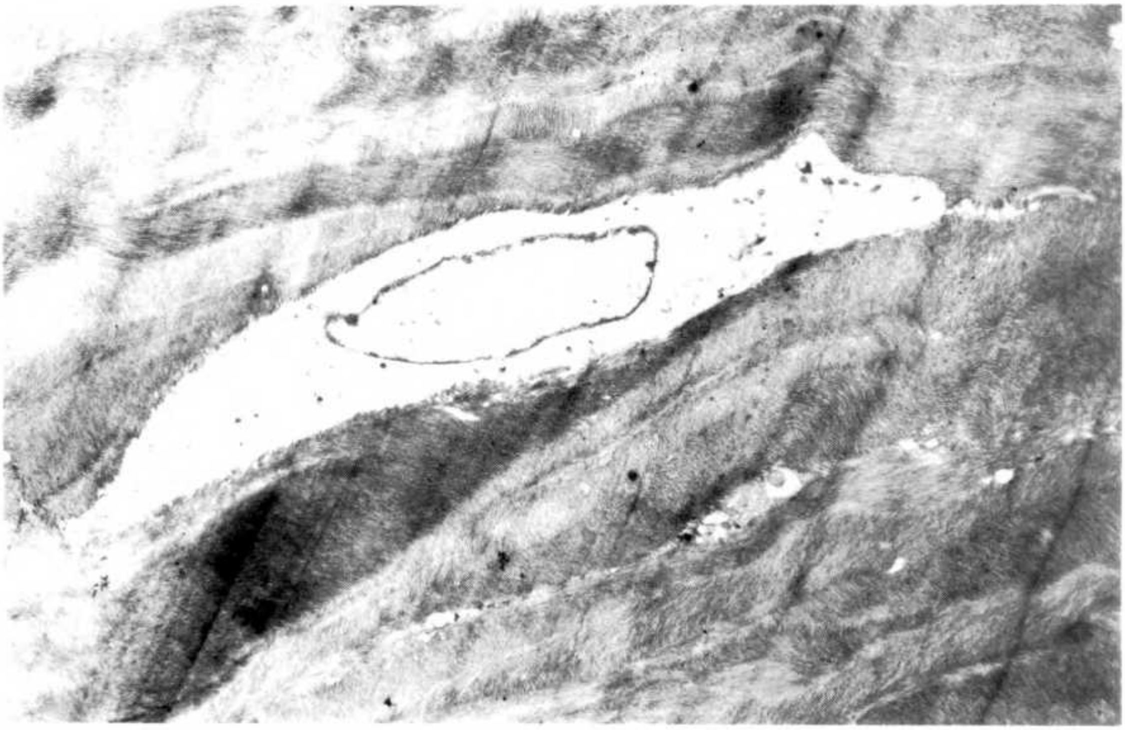

Fig. 10B *Keratocyte distended with electron-lucent vacuoles and granular debris. Nuclear membrane is present but plasmalemma has largely absorbed. (Electron micrograph, ×4610).*

by these cells, although the possibility that these changes were reactive rather than primary was acknowledged.

It is improbable that keratocyte degeneration seen in our case is merely a sequel to recurrent erosions of the epithelium and Bowman's layer, since the main biopsy was taken towards the upper periphery of the lesion, where such occurrences are rare. Moreover, Rice and his co-workers[5] observed only inconstant keratocyte injury even in long-standing cases of Reis-Bücklers's dystrophy, in spite of recurrent epithelial breakdown and disintegration of Bowman's layer. Nor does it appear that calcification of the Bowman's layer would in itself account for such severe changes in the keratocytes, since no gross abnormality of the keratocytes was noted either by Koseki[6] in his electron microscopic study of the calcified anterior stroma in a patient with band keratopathy and uveitis, or by Ticho and his coworkers[7] in their examination under light microscopy of a keratectomy specimen from a patient with primary calcific band-shaped keratopathy. Artefactual change may be excluded on the grounds that cytological preservation of the specimen was otherwise adequate and that the changes were seen throughout the biopsy. Keratocyte degeneration in this case may have been a response to a precursory unknown noxious stimulus, but there is no other clinical or ultrastructural evidence to support this contention. Thus, disease of the corneal keratocytes of the anterior stroma cannot be excluded as the primary disorder in our patient. It may be further hypothesised that such a breakdown of the superficial keratocyte system, liberating lysosomal enzymes including phosphatases, could produce a local increase in phosphate which, combined with calcium, has impregnated the Bowman's layer.

Dehiscence of this layer probably played a role in the natural exfoliation of the opacity, causing recurrent erosions. These attacks stopped spontaneously on the right side, presumably when most of the opacity had been eroded, and they have ceased on the left side following superficial keratectomy. We found no ultrastructural correlation with the greyish bars outlining the polygons seen in the opacity clinically. This is in contrast with the observations made by Tripathi and Bron,[8] who in their case of secondary anterior crocodile shagreen of Vogt found calcified folds of the Bowman layer, corresponding with the mosaic.

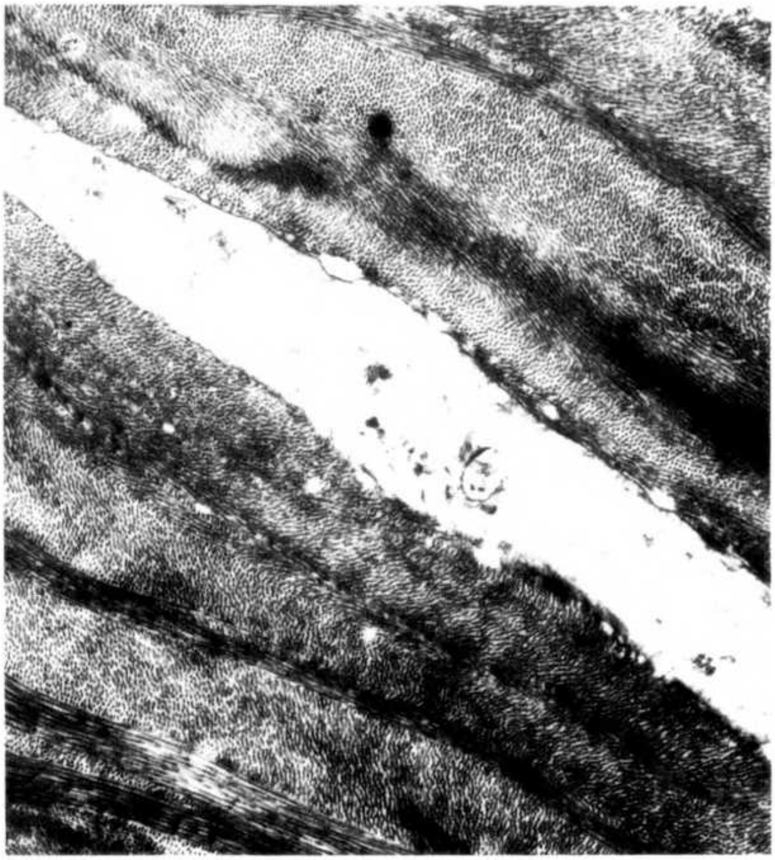

Fig. 10C *A 'ghost' keratocyte in which a few organelles and tonofibrils remain. (Electron micrograph, ×8415).*

Mr R. Cousins, the Charles Clifford Dental Hospital, Sheffield, was responsible for the photomicrographs.

This work was supported by a grant from the British National Committee for the Prevention of Blindness.

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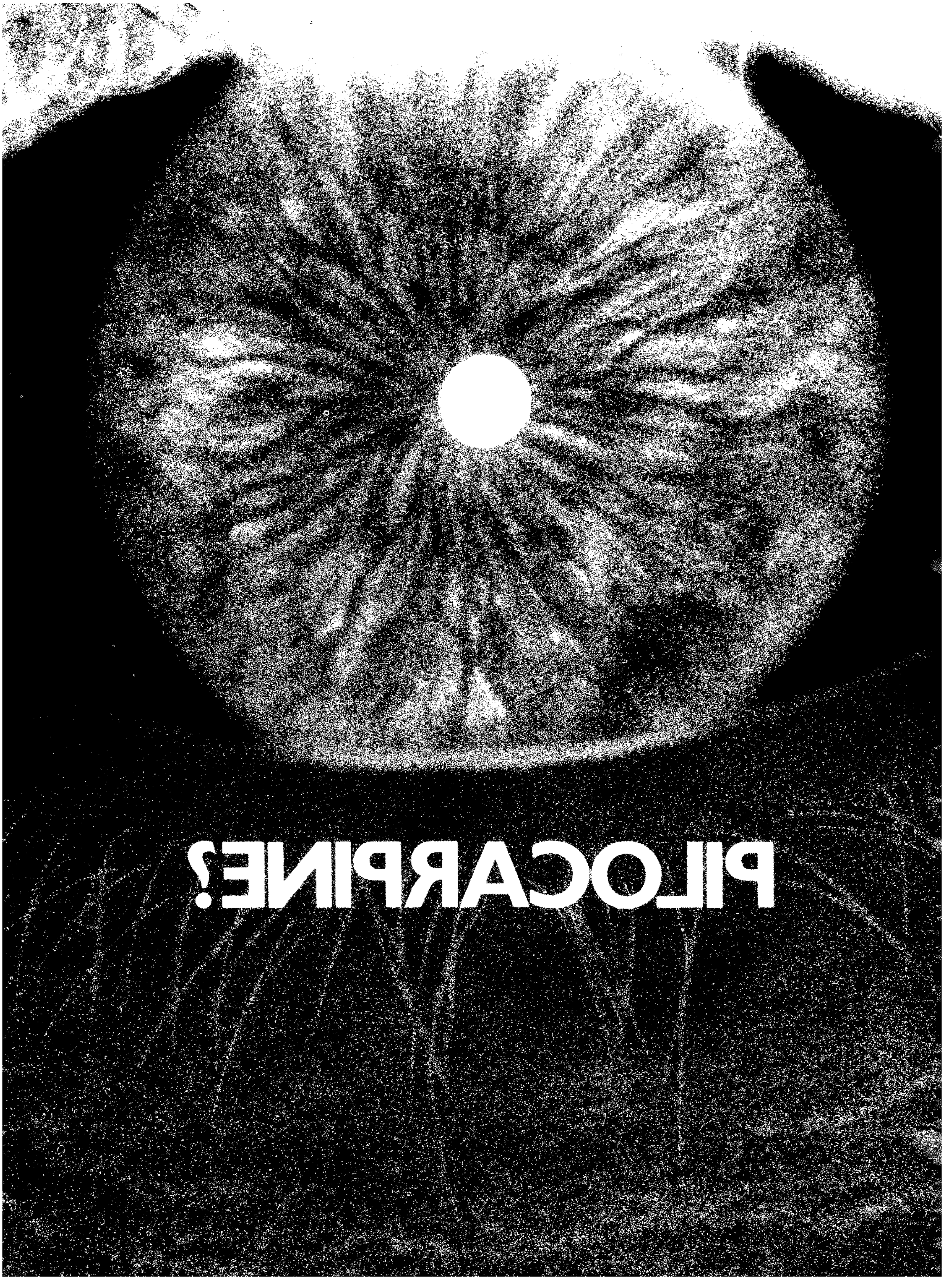
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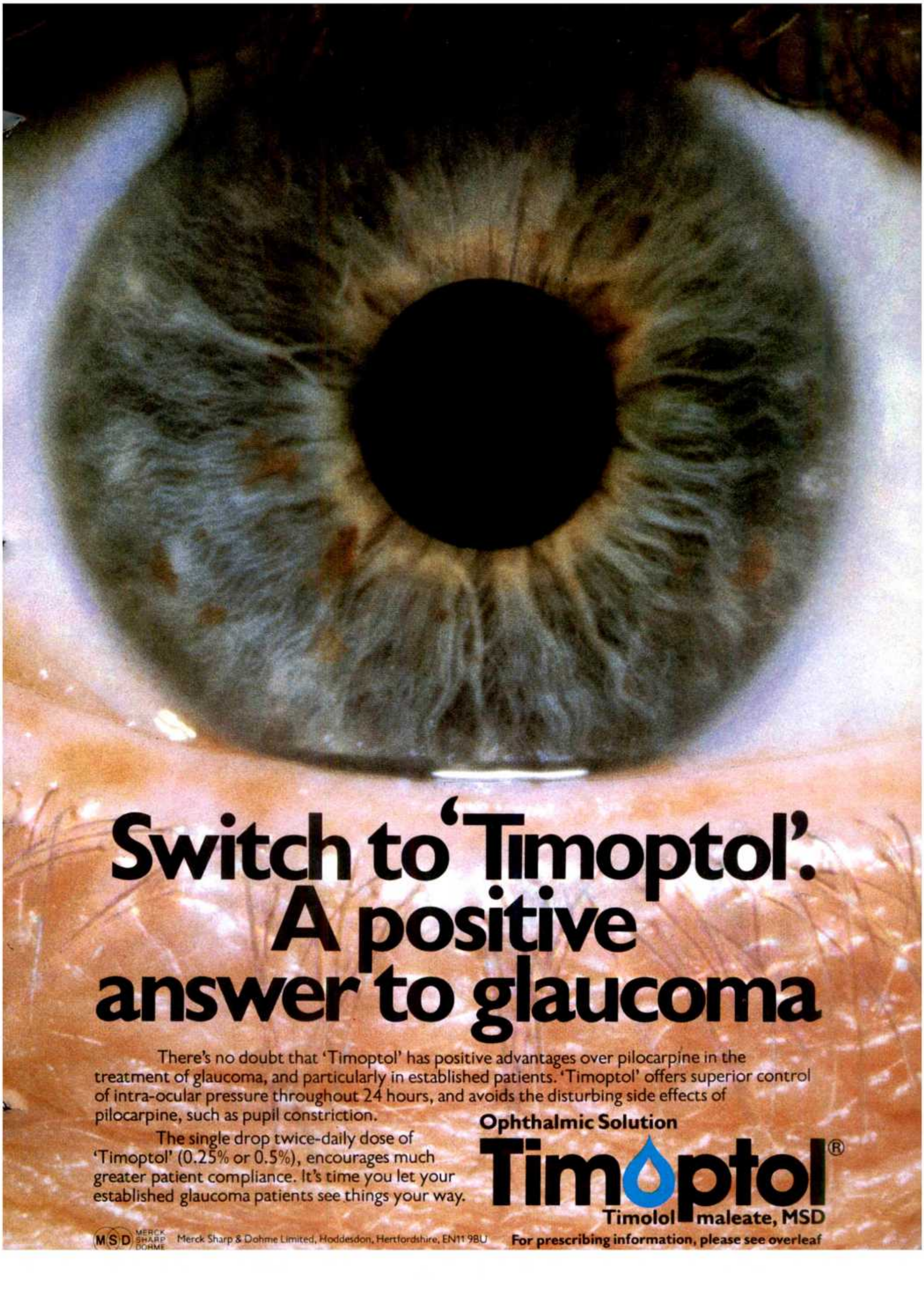

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British Journal of Ophthalmology, 1982, **66**, 317–319

Immune electron microscopy and a cultural test in the diagnosis of adenovirus ocular infection

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SUMMARY Immune electron microscopy (IEM) and virus isolation in cell culture were compared in the diagnosis of adenovirus ocular infection during an outbreak of the disease in 1979. Eleven of 14 patients with a keratoconjunctivitis clinically indicative of adenovirus infection had IEM evidence of adenovirus infection or had the virus isolated from ocular swabs. The IEM was positive in 8 patients. Virus was isolated from 10 patients. IEM was positive in one culture-negative patient. Since IEM provides a rapid and sensitive method for the detection of adenovirus in human tears, it may be a valuable diagnostic tool for the clinician.

Sporadic cases and outbreaks of acute follicular conjunctivitis caused by various types of adenovirus are well known all over the world. The most frequently used laboratory tests for the diagnosis of adenovirus ocular infection are cultural tests for virus isolation and the complement fixation test (CFT). Gibson and coworkers[1] observed no significant difference between these 2 tests when the conjunctival swabbings for the cultural test and the sera for CFT were collected at the optimum times. However, these tests are slow and require weeks for their performance. Sometimes a rapid diagnosis is desirable. Imre and coworkers[2] and Schwartz and coworkers[3] used an immunofluorescent technique to demonstrate adenoviral antigens in epithelial cells on conjunctival scrapings. An experienced collector is essential for the collection of good specimens. When good specimens are collected, this is a reliable and rapid diagnostic technique. We wanted to investigate if immune electron microscopy (IEM) of human tears could be of any help for a rapid diagnosis of adenovirus ocular infection.

After we finished this study Boerner and coworkers[4] reported the use of the pseudoreplica technique for the detection of adenovirus in human tears by electron microscopy. In their study 9 of 34 patients with a keratoconjunctivitis clinical indicative of adenovirus infection had EM evidence of adenovirus infection.

Materials and methods

Patients attending the Rotterdam Eye Clinic in 1979 with a keratoconjunctivitis suggestive of an adenovirus infection were included in this study.

Immune electron microscopy. Tears of patients were collected at the lateral canthus in a 100 μl capillette (Lab. Mannheim GMBH). The capillette was held horizontal to collect the tears. Mostly about 50–100 μl of tears was collected. The ends were sealed with parafilm laboratory film (American Can Company) and were sent immediately to the laboratory or refrigerated at 4°C before transportation. IEM was performed according to the method of Derrick,[5] modified by Milne and Luisoni.[6]

Cultural test. A dry swab (Exogen Ltd, Glasgow) was wiped firmly, with rotation of the swab, in the lower fornix and then placed in a transport medium (buffered salt solution with gentamicin and amphotericin B) and sent immediately to the laboratory or kept at 4°C before transport. Each specimen was inoculated into cultures of embryonic fibroblasts and of human epitheloid cell line. The inoculated cell cultures were examinated at regular intervals for the presence of cytopathic effect. Incubation time went up to 21 days, including a blind passage for the human epithelioid cell line. When a cytopathic effect was found, a second passage of the tissue culture was done. After fixation the monolayer was transferred to a slide and stained with haematoxylin-eosin to study the characteristic intranuclear inclusions.

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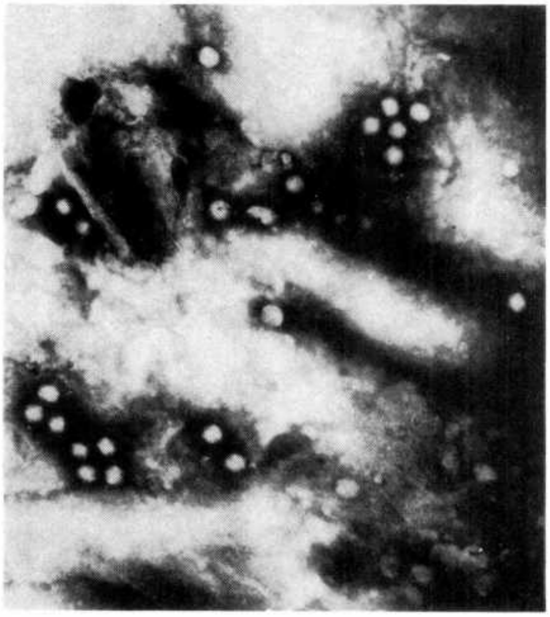

Fig. 1 *Adenovirus in human tears. (×45 000).*

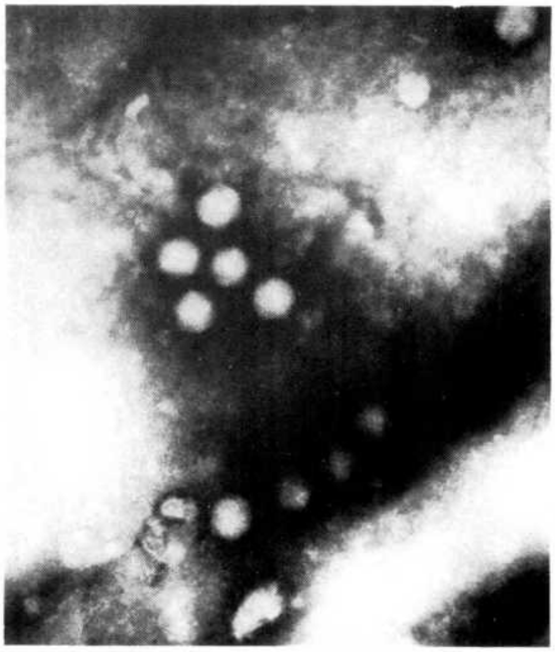

Fig. 2 *Adenovirus in human tears. (×95 000).*

Results

Immune electron microscopy. Fifteen tear samples of 14 patients were collected. Of these 8 were positive for adenovirus (Figs. 1 and 2). The tear samples were mostly collected during the first week of the infection. Of one patient, working in the virology department, tears were collected on the first day of symptoms. The IEM was negative. Two days later the IEM was positive for adenovirus. This is the only patient on whom we repeated the IEM after a negative result at the first examination. As we did not see any other patient on the first day of symptoms, we included this patient in the IEM-positive group.

Virus isolation. Fourteen specimens were collected of 14 patients at the same time as the tears for IEM. Adenovirus was isolated from 10 patients. The specimen of the patient working in the virology department, which was collected on the first day of symptoms, was positive for adenovirus. It yielded adenovirus 37.[7 8] The adenovirus with which she was working before she got her infection was type 8. The adenovirus of the other patients included in this study were not all typed, mainly because it was extremely difficult to obtain infectious virus on passaging the virus after the isolation.

Discussion

IEM and cell culture were compared in the diagnosis of adenovirus ocular infection. IEM was positive in 8 of 14 patients. Virus was isolated in 10 of the 14 patients. One patient was positive for IEM and negative for adenovirus isolation. In one patient the IEM was negative on the first day of symptoms but positive 2 days later. Because the IEM is a rapid technique one can repeat the test after some days. Since IEM provides a rapid and sensitive method for the detection of adenovirus in human tears, it may be a valuable diagnostic tool for the clinician.

We are grateful to Professor Dr H. E. Henkes for his encouragement to undertake this study.

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British Journal of Ophthalmology, 1982, **66**, 320–321

Ovulation-associated uveitis

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SUMMARY A case of anterior uveitis regularly recurring with ovulation is reported.

Uveitis is one of the diseases in which a variety of aetiological and associated factors play a role, and conclusive evidence on the precise cause is often not established. This is also true of hormonal influences. However, we have observed a remarkable case of an association between sex hormones and recurring uveitis.

Case report

A female patient aged 25 came to our hospital complaining of recurrent redness and defective vision in both eyes of 6 months' duration. The history revealed that this complaint recurred regularly about 12 days before the onset of menstrual bleeding. The periods were regular and there was no dysmenorrhoea. The patient had been married for one and a half years and was nulliparous. She had recently discontinued the use of Anovlar (norethisterone acetate 4 mg, ethinyloestradiol 50 μg) for contraception.

Ocular examination showed a visual acuity of 6/12 in each eye. There was circumcorneal ciliary congestion in both eyes. A few fine keratic precipitates and grade I aqueous flare were also seen. Both fundi were normal. The intraocular pressure was normal. Gynaecological examination showed an anteverted, normal-sized uterus; the fornices were free and the cervix was healthy. Further investigations gave a normal haemogram, a nonreactive VDRL, and showed nothing abnormal in urine and stools. Radiographs of the paranasal sinuses and chest failed to reveal any lesion.

Endometrial biopsy showed a secretory phase. Biochemical and hormonal investigations for plasma progesterone levels were carried out. The findings were as follows: on the 6th day of the cycle, 0·20 ng/ml (0·6 nmol/l); 13th day of the cycle, 2·73 ng/ml (8·7 nmol/l); 20th day of the cycle, 8·79 ng/ml (27·9 nmol/l); 26th day of the cycle, 4·94 ng/ml (15·7 nmol/l).

The patient was given steroids and atropine locally and subconjunctivally. The symptoms subsided.

After some months the patient returned and reported that following the last attack, when she was treated, she had two others at regular intervals. She could not come for treatment then. She had coincidentally resumed the use of Anovlar and was happily surprised that since then there had been no more attacks.

She is at present free of symptoms, and ocular examination reveals no abnormality.

Discussion

Uveitis is well known to be influenced by or connected with various endocrine factors. Yet its relationship with sex hormones is neither amply documented nor well substantiated. Cant[1] has reported a case of menstrual red eye. It was in fact a hypopyon iritis in one eye occurring consistently for 3 years with both regular and irregular menstrual cycles. The various investigations were normal but for an eosinophilia. Another case[2] was an incidental finding of an irritable red eye in a patient who stated it had been a regular feature before the beginning of every period over the preceding 20 years. The patient showed signs of corneal involvement and impaired vision in the left eye. The condition responded to antibiotics and mydriatics. Neither of these reports, however, describe the effect of hormone therapy on the condition.

Heaton[3] studied many patients with uveitis and thought that some of these cases should be included in the premenstrual syndrome described by Greene and Dalton.[4]

The distribution of mast cells in the normal eyes of experimental animals such as rats and guinea-pigs was studied by Smelser and Silver.[5] They found that a large number of mast cells were present in the

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posterior choroid, the distribution following the uveal vessels. A high concentration was constantly seen along the long posterior ciliary arteries. In the deeper parts of the ciliary body there was a ribbon-like band completely round the eye. The ciliary processes contain very few mast cells and these are almost absent in the iris. Parish, cited by Selye,[6] concluded that mast cells are mediators of changes occurring in inflammation; they provide a reserve of material readily available in sudden physiological stresses or damage to the tissues. In the rabbit's eye the mast cells have been shown to undergo degranulation as a result of experimentally induced hypersensitivity (type I of Gell and Coombs[7]). In acute inflammation the mast cell number falls and in chronic inflammations it rises, according to Gunther, cited by Selye.[8]

The mast cells are found in the female genital tract during the follicular phase. The endometrial mast cells degranulate premenstrually and gradually regenerate in the rest of the cycle. No mention of any ocular change has been made.[9] Intrauterine contraceptive devices do not cause any change in mast cell content of the genital tract.[10]

In this case the nonoccurrence of uveitis during the anovulatory cycles after the use of a contraceptive proved the relationship between ovulation and uveitis.

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British Journal of Ophthalmology, 1982, **66**, 322–325

Hyperfluorescent dots in the ciliary body band in patients with granulomatous uveitis

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SUMMARY Fluorescein gonioangiography was performed in 4 eyes of 4 patients with ocular sarcoidosis and in an eye of a patient with presumptive tuberculous anterior uveitis. Small discrete whitish lesions in the ciliary body band near the iris root showed hyperfluorescence shortly after fluorescein injection. These hyperfluorescent dots seemed to be pathognomonic changes in cases with granulomatous uveitis.

In 1965 Eisner[1] observed the anterior chamber angle after fluorescein injection and reported that staining of the ciliary body band occurred in cases of cyclitis. In 1980 the author[2] presented gonioangiograms which showed vigorous leakage of the dye from the angle recess into the anterior chamber in a case of Behçet's disease during an attack of uveitis. To the best of my knowledge there are no studies of fluorescein gonioangiography in cases of granulomatous uveitis. The purpose of this communication is to report gonioangiographic findings in such cases.

Patients and methods

The same method of fluorescein gonioangiography as previously described[2] was used in this study. Four eyes of 4 patients with ocular sarcoidosis and one eye of a patient with presumptive tuberculous anterior uveitis were selected from our clinic for this study. All the patients had a complete eye examination. Those with a history of ocular surgery and ocular trauma and with abnormal intraocular pressure were excluded. In all 4 patients with ocular sarcoidosis the diagnosis was established by a biopsy of either conjunctival follicles or scalene nodes.

Case reports

OCULAR SARCOIDOSIS

Case 1. A 21-year-old male was diagnosed as having bilateral hilar lymphadenopathy and was referred to our clinic. Vision was 20/20 without correction in both eyes. Biomicroscopy showed neither keratic precipitates nor flare in the anterior chamber in both eyes. The iris was normal in appearance in both eyes. He had complained of no eye symptoms. However, ophthalmoscopy revealed 'candle wax' drippings along the peripheral retinal vessels in both eyes. The intraocular pressure was 12 mmHg in the right eye and 11 mmHg in the left. Gonioscopy revealed small whitish lesions in the ciliary body band near the iris root associated with discrete gelatinous nodular lesions in the filtration angle in both eyes. Fluorescein gonioangiography (Fig. 1) in the lower nasal quadrant of the right eye was performed, and it showed soon after the fluorescein injection a hyperfluorescent dot corresponding to the whitish lesion in the ciliary body band. The gelatinous nodular lesions in the filtration angle showed relative hyperfluorescence in the late phase of the angiography. A tuberculin skin test was negative, and the diagnosis of sarcoidosis was confirmed by a biopsy of the scalene nodes. Prednisone 60 mg per day by mouth and 1% sodium betamethasone eye drops 5 times a day were instituted.

Case 2. A 19-year-old male was diagnosed as having bilateral lymphadenopathy and was referred to our clinic. Vision was 20/20 without correction in both eyes. The applanation pressure was 15 mmHg in the right eye and 14 mmHg in the left. Biomicroscopy showed neither keratic precipitates nor flare in the anterior chamber in both eyes. The iris was normal in appearance in both eyes. Ophthalmoscopy showed nothing abnormal in both eyes. He had complained of no eye symptoms. However, gonioscopy revealed small whitish lesions in the ciliary body band near the iris root in both eyes. Fluorescein gonioangiography (Fig. 2) in the lower nasal quadrant of the right eye revealed shortly after fluorescein injection a

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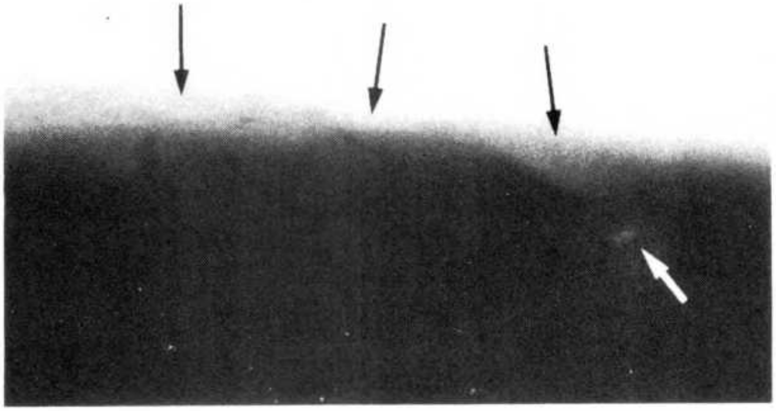

Fig. 1 *Fluorescein gonioangiogram in a 21-year-old male with ocular sarcoidosis (case 1) showing at 70 seconds a hyperfluorescent dot (white arrow) and relative hyperfluorescence (black arrows) corresponding to the gelatinous nodular lesions in the filtration angle.*

hyperfluorescent dot corresponding to the whitish lesion in the ciliary body band. A tuberculin skin test was negative, and the diagnosis of sarcoidosis was confirmed by a biopsy of the conjunctival follicles. 1% sodium betamethasone instillation 5 times a day was instituted.

Case 3. A 20-year-old male was diagnosed as having bilateral hilar lymphadenopathy and was referred to our clinic. Vision was 20/20 with correction of myopia in both eyes. Biomicroscopy showed neither keratic precipitates nor flare in the anterior chamber in both eyes. The iris was normal in appearance in both eyes. Ophthalmoscopy showed nothing abnormal in both eyes. He had complained of no eye symptoms. However, gonioscopy revealed small whitish lesions in the ciliary body band near the iris root. Fluorescein gonioangiography (Fig. 3) in the lower temporal quadrant of the right eye revealed shortly after fluorescein injection a hyperfluorescent dot corresponding to the whitish lesion in the ciliary body band. A tuberculin skin test was negative, and the diagnosis of sarcoidosis was confirmed by a biopsy of the scalene nodes. 1% sodium betamethasone instillation 5 times a day was instituted.

Case 4. A 38-year-old male was observed to have enlarged hilar glands on a chest x-ray film and was referred to our clinic. Vision was 20/20 with myopic correction in both eyes. The applanation pressure was 11 mmHg in both eyes. Biomicroscopy showed neither keratic precipitates nor flare in the anterior chamber in both eyes. The iris was normal in appearance in both eyes. He had complained of no eye symptoms. However, gonioscopy revealed several small whitish lesions in the ciliary body band near the iris root. Fluorescein gonioangiography (Fig. 4) in the lower nasal quadrant of the right eye

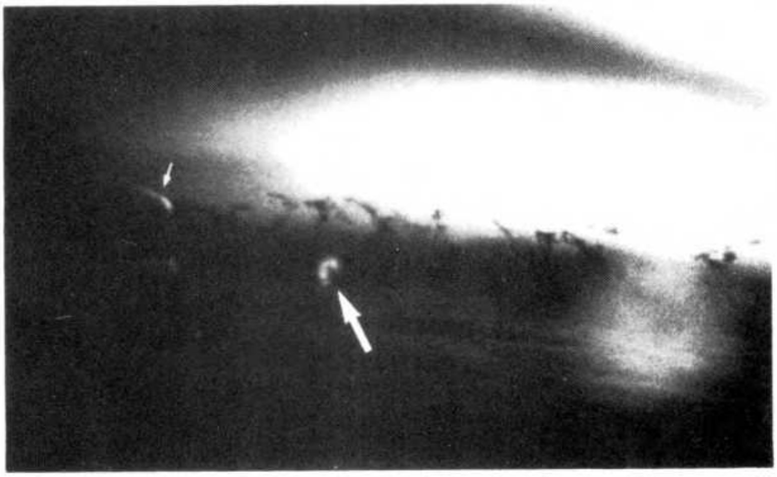

Fig. 2 *Fluorescein gonioangiogram in a 19-year-old male with ocular sarcoidosis (case 2) 25 s after fluorescein injection showing a hyperfluorescent dot (large white arrow) in the ciliary body band near the iris root. The angle vessel is also fluorescent (small white arrow).*

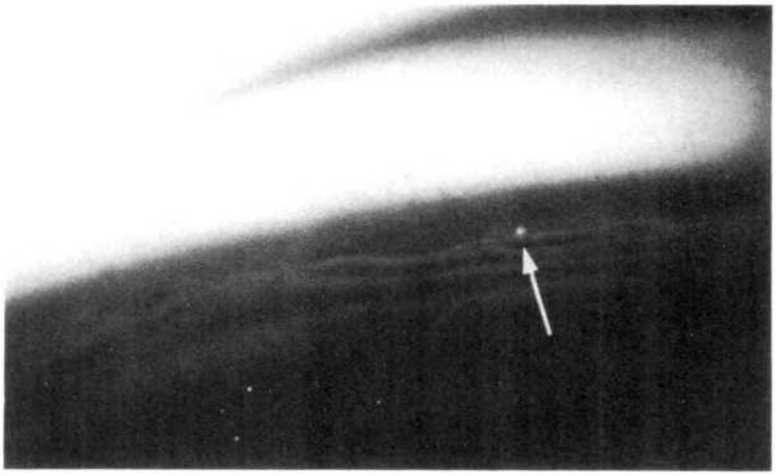

Fig. 3 *Fluorescein gonioangiogram in a 20-year-old male with ocular sarcoidosis (case 3) 30 s after fluorescein injection showing a hyperfluorescent dot (white arrow) in the ciliary body band near the iris root.*

revealed shortly after fluorescein injection hyperfluorescent dots corresponding to the whitish lesions in the ciliary body band. A tuberculin skin test was negative, and the diagnosis of sarcoidosis was confirmed by a biopsy of the scalene nodes. 1% sodium betamethasone instillation 5 times a day was instituted.

PRESUMPTIVE TUBERCULOUS ANTERIOR UVEITIS
Case 5. A 17-year-old female had complained of blurred vision in both eyes several weeks previously and was seen by an ophthalmologist. She was referred to our clinic with the diagnosis of iritis in both eyes. Vision was 20/20 with myopic correction in both eyes. The applanation pressure was 13 mmHg in the right eye and 16 mmHg in the left. Biomicroscopy revealed not only keratic precipitates but also flare and cells in the anterior chamber in both eyes. The iris was normal in appearance in both eyes. Ophthalmoscopy showed nothing abnormal in both eyes. No abnormal findings were observed on a chest *x*-ray film. A tuberculin skin test was strongly positive. Gonioscopy revealed numerous small whitish lesions in the ciliary body band near the iris root in both eyes. Fluorescein gonioangiography (Fig. 5) in the lower temporal quadrant of the left eye revealed shortly after fluorescein injection numerous hyperfluorescent dots corresponding to the whitish lesions in the ciliary body band. In the late phase of the gonioangiography the ciliary body band was stained. In this case a diagnosis of presumptive tuberculous anterior uveitis was made. Isoniazid 250 mg per day was given by mouth for about 8 weeks, resulting in gradual subsidence of the inflammation.

Discussion

François[3] observed both the whitish lesions in the ciliary body band and the gelatinous nodular lesions in the filtration angle in a case of acute iridocyclitis. In his Fig. 1 the whitish lesions in the ciliary body band near the visible edge of the iris are clearly

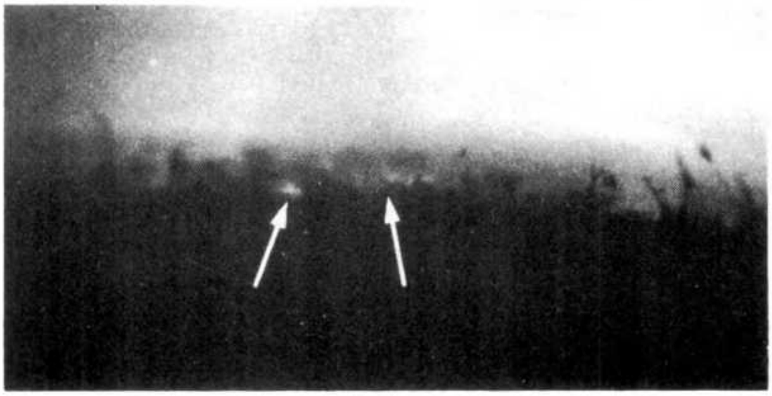

Fig. 4 *Fluorescein gonioangiogram in a 38-year-old male with ocular sarcoidosis (case 4) 20 s after fluorescein injection showing several hyperfluorescent dots (white arrows) in the ciliary body band near the iris root.*

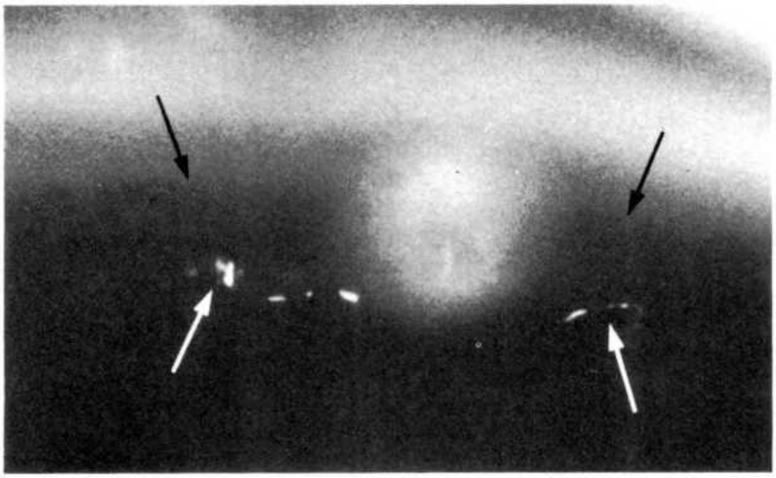

Fig. 5 *Fluorescein gonioangiogram in a 17-year-old female with presumptive tuberculous anterior uveitis, 10 s after fluorescein injection showing numerous hyperfluorescent dots in the ciliary body band near the iris root. White arrows indicate the iris root and black arrows the scleral spur.*

demonstrated. Brockhurst *et al.*[4] observed the nodular lesions in the angle in cases of granulomatous uveitis. Because of difficulties in performing tissue biopsies of these lesions in the angle there are few clinicopathological studies of them. Thus the pathogenesis of these lesions in the angle has been a matter of speculation. In the present study by means of fluorescein gonioangiography the whitish lesions in the ciliary body band near the iris root were clearly distinguished from the gelatinous nodular lesions in the filtration angle. The whitish lesions showing hyperfluorescence shortly after fluorescein injection in all 5 cases studied were firmly considered to be granulomas in the ciliary body band. On the other hand the gelatinous nodular lesions in the filtration angle showing relative hyperfluorescence in the late phase of the angiography in case 1 were thought to be not granulomas but exudates. However, further studies by means of gonioscopy, fluorescein gonioangiography, and histological methods should be performed.

In all four cases with ocular sarcoidosis (cases 1–4) studied both the cornea and the aqueous were clear despite apparent changes in the angle. In addition in all 5 cases biomicroscopy revealed neither Koeppe nor Busacca nodules in the iris. In other words, in all cases studied the changes in the ciliary body band preceded that in the iris. As cited by Tronocoso,[5] Moreu reported in 2 cases of tuberculous uveitis that tuberculomas started in the ciliary body band rather than in the iris. Chandler and Grant[6] pointed out that in some cases of uveitis there may be no keratic precipitates and no cells in the aqueous but changes in the angle; they have stressed the importance of gonioscopy in such cases. The evidence obtained in the present study strongly supports their suggestion.

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British Journal of Ophthalmology, 1982, **66**, 326–331

Subretinal and disc neovascularisation in serpiginous choroiditis

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SUMMARY Three out of 15 patients with serpiginous choroiditis who have been followed up for 1 to 10 years (mean 4·9 years) developed subretinal neovascularisation in the macula. In one eye new vessels were treated with argon laser without attaining permanent obliteration, in the second eye the neovascular membrane was regarded as untreatable because it was under the fovea, and in the third eye new vessels became obliterated spontaneously after atrophy of the surrounding choriocapillaris and the pigment epithelium of the retina. In a fourth patient disc new vessels were seen at the active stage of serpiginous choroiditis; these new vessels disappeared after scarring of the initial chorioretinal lesions.

Postinflammatory, degenerative, traumatic, and iatrogenic defects in the Bruch's membrane and the pigment epithelium of the retina may result in subretinal neovascularisation, particularly in the macula and around the optic disc. In serpiginous choroiditis subretinal neovascularisation has been regarded as unusual because subretinal new vessels were not seen in the earlier follow-up studies on this disease.[1–3] Recently, however, Jampol *et al.*[4] described 3 patients with serpiginous choroiditis and subretinal neovascularisation. Here we report another 3 patients with subretinal new vessels, and one patient who developed disc new vessels at the active stage of serpiginous choroiditis.

Patients and methods

Fifteen patient suffering from serpiginous choroiditis were followed up by the authors for 1 to 10 years (mean 4·9 years). The patients were examined by indirect ophthalmoscopy and slit-lamp biomicroscopy with a Goldmann contact lens. Fundus photographs and fluorescein angiograms were performed on all patients on several occasions. During the follow-up subretinal new vessels were discovered in 3 eyes and disc new vessels in one eye.

CASE REPORTS

Case 1. A man aged 52 years was initially seen by the authors in 1976 because of a recurrent serpiginous lesion in the right papillomacular area. At that time there were old scars nasal to the disc and along the superior temporal vessels in the right eye and in the left macula. Sixteen months later he reappeared because of blurring of vision in the right eye. The visual acuity was 6/6, but ophthalmoscopy showed a new greyish subretinal lesion and a small subretinal haemorrhage adjacent to the previous scar. By fluorescein angiography, subretinal neovascular membrane was discovered (Fig. 1A). After photocoagulation with argon laser the new vessels seemed to disappear (Fig. 1B), but 2 months after the initial treatment some patent new vessels were visible again (Fig. 1C). In spite of successive treatments new branches of neovascularisation reappeared (Fig. 1D), until finally for about a year later the whole macula became involved, with loss of the central vision.

Case 2. A woman aged 29 years was initially seen in 1976 because of fresh serpiginous choroiditis in the right eye (Fig. 2A). Since then several recurrences have been discovered in both eyes. Seven months after the initial examination the patient reported deterioration in the vision of the right eye. The visual acuity was 6/12, and subretinal new vessels were discovered by fluorescein angiography between the old scars under the fovea (Figs. 2B, C). The lesion was regarded as untreatable. Within 3 months the visual acuity decreased to counting fingers.

Case 3. A woman aged 54 years was initially examined in 1976 because of a fresh serpiginous lesion in the right macula. In the left eye there was a

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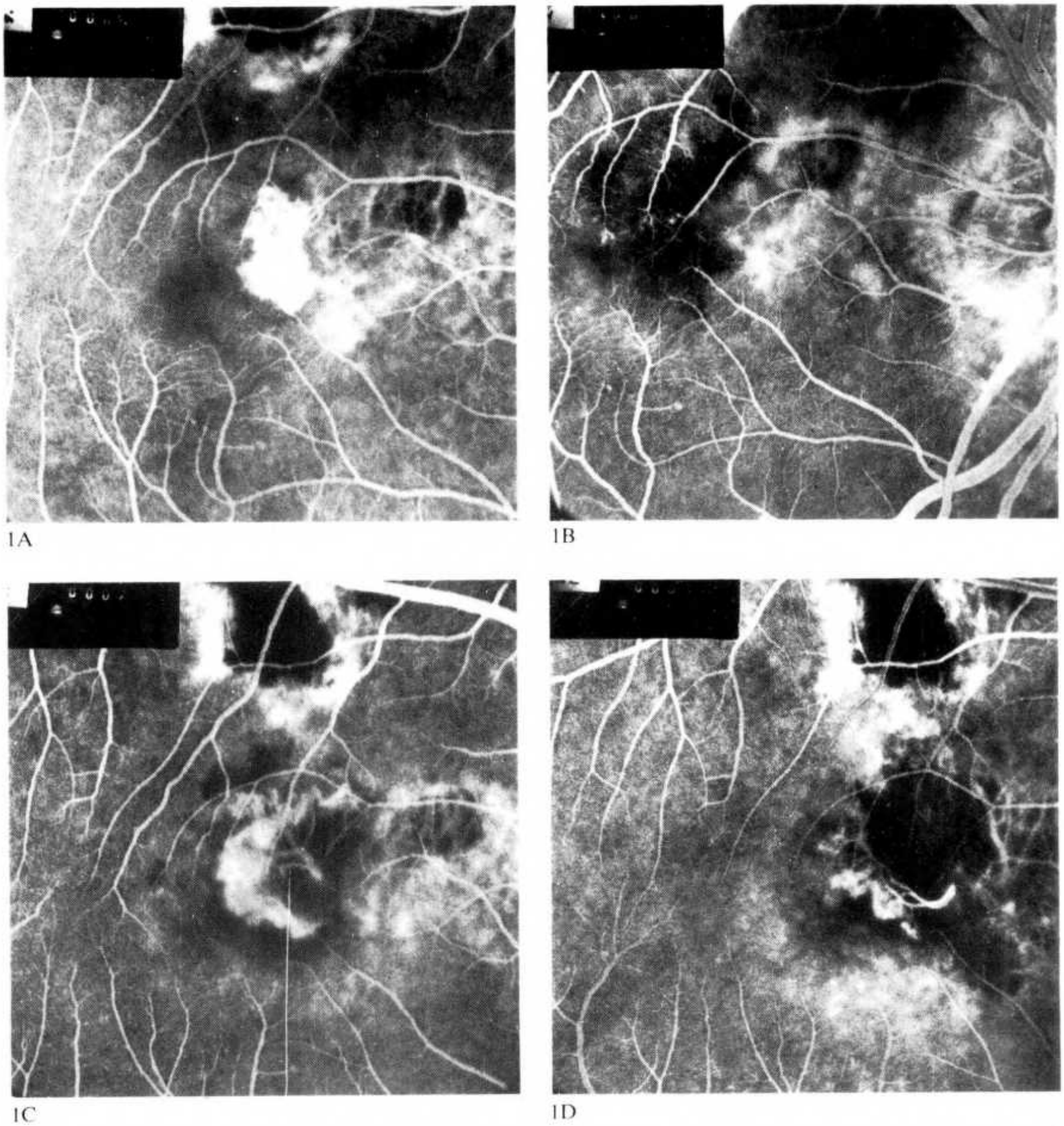


Fig. 1 *Patient 1, right eye.* (A) *Subretinal neovascular membrane adjacent to an atrophic scar in the papillomacular area.* (B) *One month after photocoagulation; no new vessels visible.* (C) *Three weeks later neovascular membrane with large leading vessels visible again.* (D) *Five months later after several treatments with argon laser; a small neovascular tuft with a new leading vessel open.*

large atrophic central scar with a small island of preserved macular tissue and a visual acuity of 6/6. Fluorescein angiography showed a small subretinal neovascularisation above the macula (Fig. 3A, B). After further atrophy of the choriocapillaris and the pigment epithelium these new vessels regressed spontaneously (Fig. 3C).

Case 4. A woman aged 20 years was initially seen in 1972 with serpiginous choroiditis all over the temporal fundus of the right eye. At the first

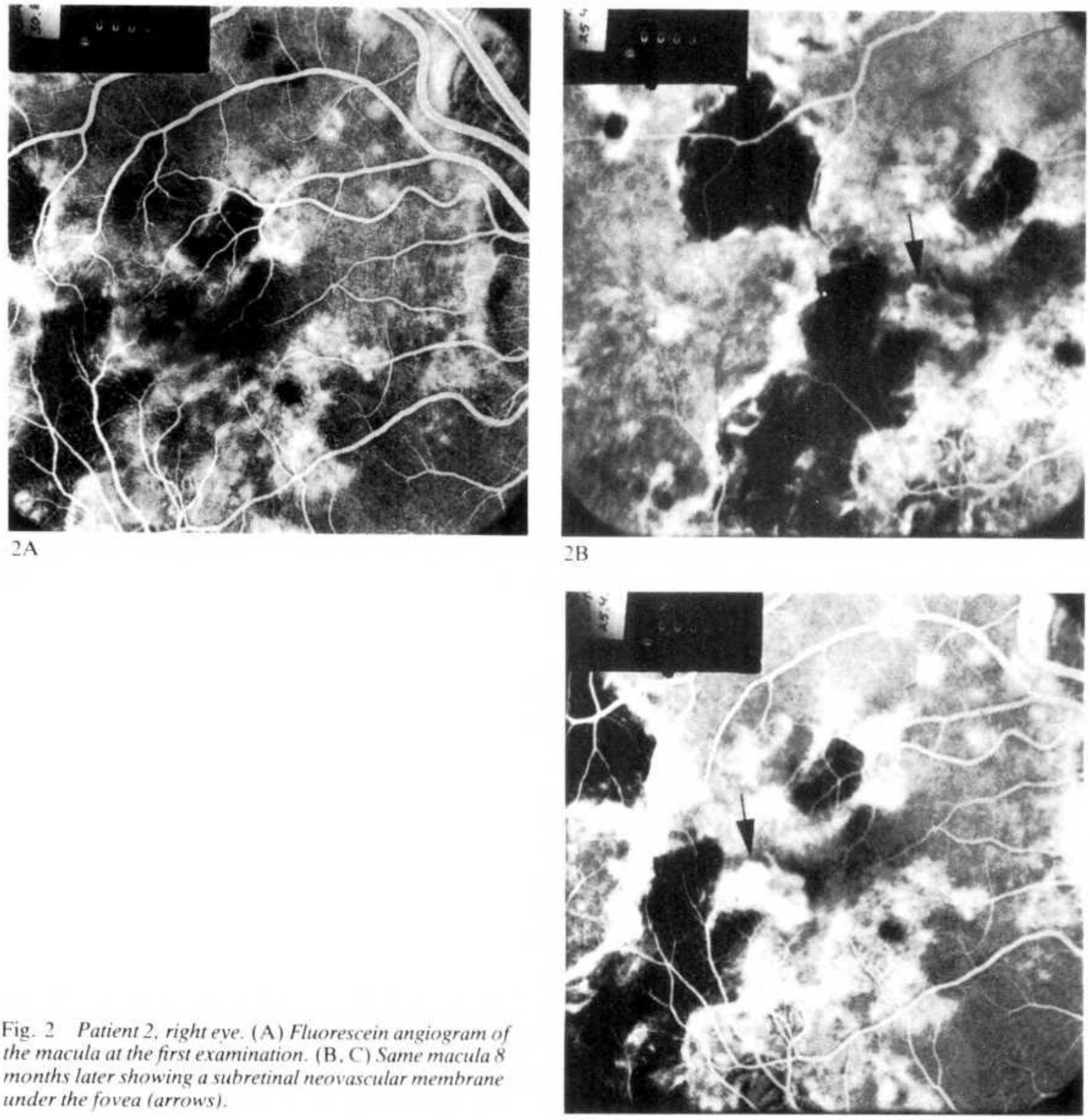


Fig. 2 *Patient 2, right eye.* (A) *Fluorescein angiogram of the macula at the first examination.* (B, C) *Same macula 8 months later showing a subretinal neovascular membrane under the fovea (arrows).*

presentation small new vessels were observed on the right optic disc (Fig. 4A, B). Six months later there were no active lesions in the fundus, and the disc new vessels had also disappeared (Fig. 4C).

Discussion

Serpiginous choroiditis is a chronic recurring disease affecting the choriocapillaris and the pigment epithelium of the retina. The aetiology is unknown, though an inflammatory cause may be suggested.[5] The disease is usually bilateral and begins at the posterior pole in the macular area or near the optic disc. These are the areas where subretinal neovascular membranes most frequently occur following degenerative or inflammatory disorders such as the presumed histoplasmosis syndrome,[6] ocular toxoplasmosis,[7] or rubella retinopathy.[8,9]

In the earlier follow-up studies on serpiginous choroiditis subretinal new vessels were not

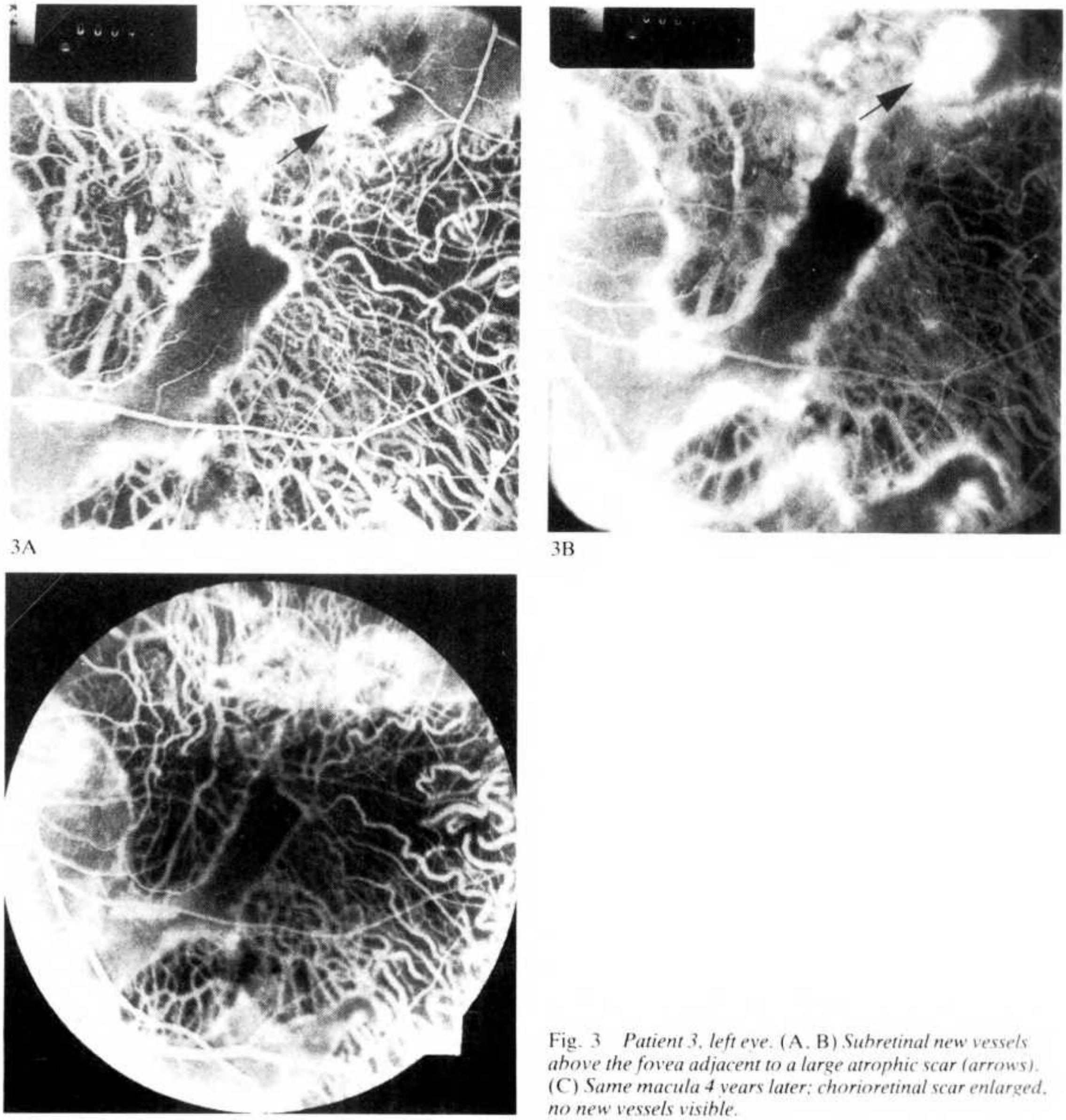
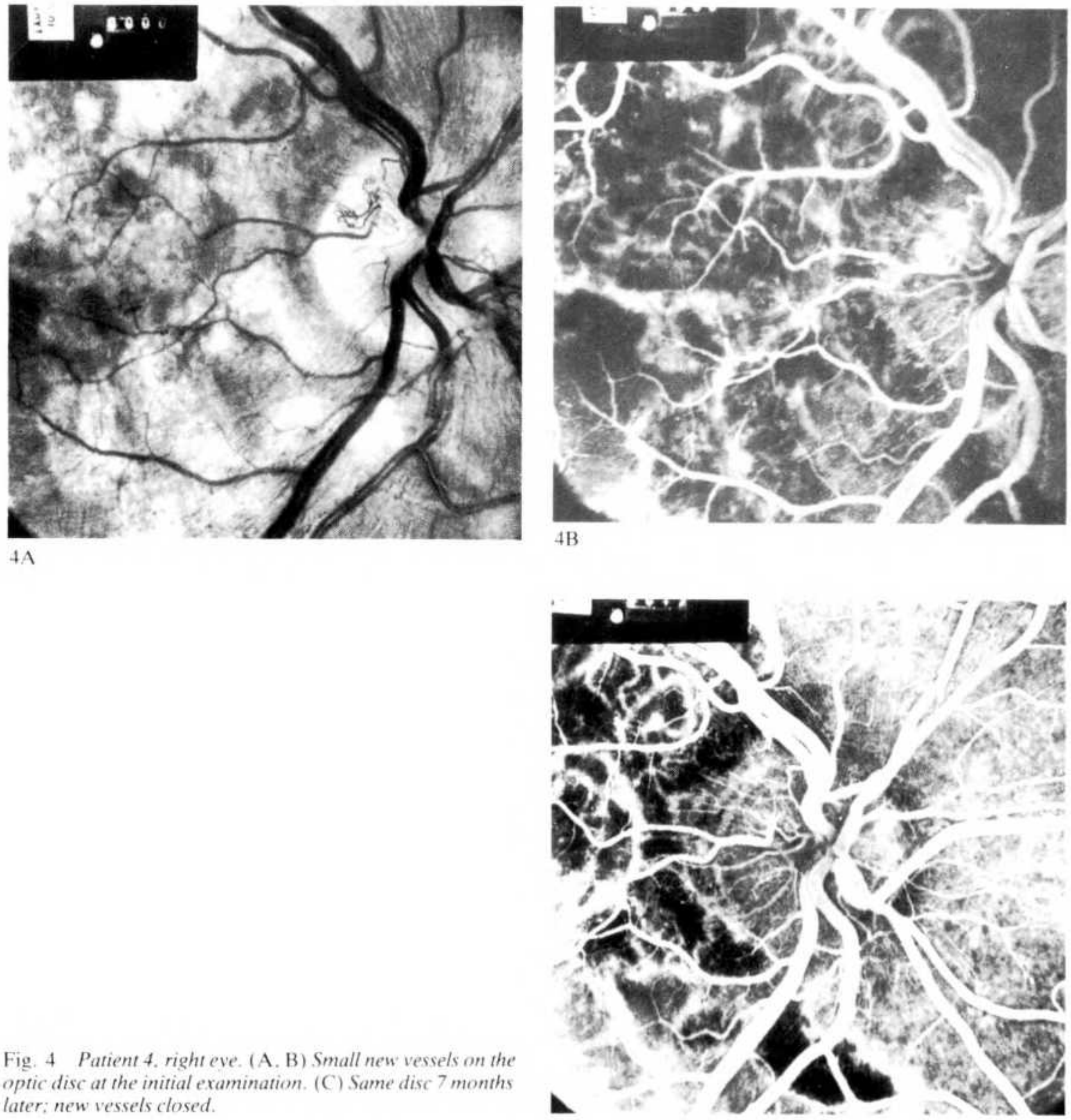


Fig. 3 *Patient 3, left eye.* (A, B) *Subretinal new vessels above the fovea adjacent to a large atrophic scar (arrows).* (C) *Same macula 4 years later: chorioretinal scar enlarged, no new vessels visible.*

observed.[1-3] The 3 eyes reported here represent, however, a considerable proportion of the eyes suffering from serpiginous choroiditis followed up by the authors.[10] By ophthalmoscopy and colour photographs subretinal new vessels were not easily discovered in these eyes, because an early subretinal neovascular membrane between the scars closely resembled a recurrent serpiginous lesion. In case 1 the presence of subretinal haemorrhage aroused the suspicion of subretinal new vessels, which were confirmed by fluorescein angiography. In the others fluorescein angiography was needed to discover the neovascularisation.

An early diagnosis of subretinal neovascularisation is of clinical importance because new vessels outside the fovea may be suitable for treatment by photocoagulation, as was shown by Jampol *et al.*,[4] who observed obliteration of the neovascular membrane in 2 of their 3 cases. In the eye reported here the treatment was not successful. If the new vessels



4A

4B

4C

Fig. 4 *Patient 4, right eye.* (A, B) *Small new vessels on the optic disc at the initial examination.* (C) *Same disc 7 months later; new vessels closed.*

appear under the small islands of normal retina between confluent scars outside the fovea, they may remain unnoticed and regress spontaneously due to progressing atrophy of the surrounding choriocapillaris and the pigment epithelium, as was seen in case 3. Similarly disc new vessels which appeared during the active stage of serpiginous choroiditis in case 4 disappeared spontaneously after scarring of the initial chorioretinal lesions.

This study was supported financially by the Paulo Foundation.

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British Journal of Ophthalmology, 1982, **66**, 332–336

Diagnosis of dyslexia by means of a new indicator of eye dominance

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SUMMARY Many dyslexic children are unable accurately to control the movements of their eyes even when they are not trying to read. This immaturity helps to explain their visual confusions. It may result from failure to develop dependable associations between retinal and ocular motor signals. These are essential to fix the true, as opposed to retinotopic, locations of objects in the outside world. We have used a new test to study retinal/ocular motor correspondence in dyslexic children and age/IQ matched normal readers. Over half the dyslexics showed unstable ocular motor dominance.

The idea that developmental dyslexia is ever the result of a primary visual disorder is not at present popular because conventional tests rarely reveal any disorder of a dyslexic's eyesight, while thousands of children with profoundly abnormal vision nevertheless learn to read successfully. Dyslexia is generally held to be a general cognitive defect rather than a perceptual one.[1]

Dyslexia is, however, often associated with abnormal movements of the eyes.[2 3] Although many people suggest that these are merely a consequence rather than a cause of reading difficulties, perhaps arising from children's inability to make sense of what they see,[4] it is now clear that many dyslexics have unusual eye movements even when they are not trying to read.

They are more likely than normal readers to show esophoria,[5] convergence insufficiency,[6] breakdown to saccadic jerks (cogwheeling) during attempts at smooth pursuit,[7] excessive numbers of regressions, and inability to maintain stable fixation when viewing sequentially illuminated light-emitting diodes.[8]

These eye movement disorders may help to explain a child's difficulties with learning to read. Reading demands highly accurate ocular motor control, together with precise monitoring of eye position, since this is essential to determine true visual direction. When we look at a letter we can estimate its true position in space only if we know the exact angle of our gaze. The positions of the images of the letter on the retinae do not reveal its correct direction in relation to the observer unless the direction in which the eyes are pointing at the time is known precisely. Retinotopic co-ordinates must be transformed into real space co-ordinates by means of extraretinal signals about eye position. Such signals are generated by the ocular motor system in the course of achieving accurate eye movements; they are then associated with retinal signals about an object in order to determine its exact whereabouts.

Monitoring of eye position is of course necessary long before reading begins, but to read successfully a new degree of precision is demanded. Dyslexics tend to lose their place on a page, and for them letters often seem to move around and reverse themselves. It is possible therefore that they fail to develop sufficiently accurate ocular motor control, and hence lack sufficient information about the direction of their gaze, to tell them precisely where their eyes are pointing when they are trying to read.

Precise movements of the eyes and hence reliable monitoring of their position may depend on the development of ocular motor dominance.[9] If the eyes are converged for near vision as when reading, the position of each eyeball is different; hence each may provide different ocular motor signals about the true direction of the same object in the outside world. To prevent confusion we probably learn to attend to the extraretinal position signals of only one eye when assessing visual direction.[10 11] The successful development of this habit in relation to foveal vision is particularly important when reading. The

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duplicated representation of the fovea and probably of the eye movements relating to it, in both visual cortices,[12 13] enhances the possibility of unreliable associations between retinal and ocular motor signals dealing with this region of the retina. Dyslexia may therefore sometimes be associated with failure to develop consistent dominance of one eye's ocular motor signals. This may lead to confusion about precisely where words and letters are positioned on a page.

Unfortunately monocular indicators of eye dominance, such as the eye preferred for using a telescope, or binocular measures relating to distance vision, such as the 'sighting eye' test, probably fail to indicate whether reliable association of the ocular motor and retinal signals which deal with foveal vision during convergence has been achieved.[6 14–16] The problem when reading, which the development of ocular motor dominance of one eye helps to solve, is that of defining visual direction when the eye position signals provided by each eye disagree. A test for eye dominance should therefore establish such conflict, if it is to be relevant to the diagnosis of dyslexia. Then, if it is shown that the associations made by ocular motor and retinal signals deriving from each eye are variable, we may conclude that the subject has failed to achieve reliable ocular motor dominance.

We have therefore modified an orthoptic test, introduced by Dunlop,[5] in order to provide conditions in which the retinal and ocular motor signals furnished by each eye do not agree with each other. We have used this test in a double-blind study of dyslexics and normal readers, and here show that 'visual' dyslexics fail to develop reliably lateralised ocular motor dominance.

Subjects and methods

Eighty children (69 boys) were referred to the Ophthalmology Department of the Royal Berkshire Hospital from 2 centres in Reading which took children with reading problems from local primary schools. We classified them as 'dyslexic' because despite having a normal performance intelligence quotient (IQ) (WISC>90) their reading age (using the Neale analysis of reading accuracy) was more than 18 months behind their chronological age. We compared the dyslexics with 80 normal readers matched according to age and performance IQ drawn from the same schools. Children were excluded if they had a history of neurological, psychiatric, or social problems.

Each child was assessed by remedial teachers according to the type of reading errors he or she made. Although these assessments were perforce subjective, attempting to indicate for teaching purposes the nature of the children's reading errors as 'visual' or 'nonvisual', neither we nor the children were informed who had been classified as dyslexic, whether visual or nonvisual, until after we had completed our ocular examinations.

We also studied a further 274 children with similar reading difficulties but for whom we do not have detailed IQ, reading age or reading error assessments.

CLINICAL EXAMINATION

A complete medical history was taken from all 434 children. Each was given ophthalmological and orthoptic examinations. The children were all asked which hand they used for writing and which foot they used for kicking; and each performed the Dunlop test 10 times.

DUNLOP TEST

The child viewed through a synoptophore 2 macular sized fusion slides (Clement Clark F9 and F10) showing a house with a central front door and different sized trees as controls. In the slide viewed by the right eye a small tree was drawn on the left of the front door; in that viewed by the left eye a large tree was placed to its right. Thus the trees were viewed in the nasal field of each eye and were therefore initially projected to the visual cortex ipsilateral to that eye. But since door and trees subtended an angle of only 3° bilaterality of these signals was likely. The subjects were asked to fixate a knob in the centre of the door. The synoptophore tubes were first adjusted so that the slides fused. The subject then saw a single house with a large tree to the right (viewed by the left eye) and a small tree to the left of the door (viewed by the right eye). The tubes were then separated; thereupon the subject's eyes diverged by up to 5° in order to preserve fusion. Within each slide the door and the tree remained fixed in relation to each other, yet subjects gained a very strong impression that one of the trees moved towards the door.

In the test the eyes were made to move in opposite directions. Ocular motor signals about lateral movements of each eye are probably organised in the hemisphere contralateral to that eye.[17] In our test the trees were viewed in the nasal field of each eye; hence retinal signals about the trees were projected to the ipsilateral hemisphere. Yet for most people movement information deriving from one eye was successfully associated with retinal signals about the tree seen by that eye, presumably employing interhemispheric connections. This gave rise to the consistent illusion that one, but only one, of the trees moved. Retinal and ocular motor signals derived from the other eye were not associated in this way, and the tree seen by the other eye did not appear to move. Hence this version of the Dunlop test seems to

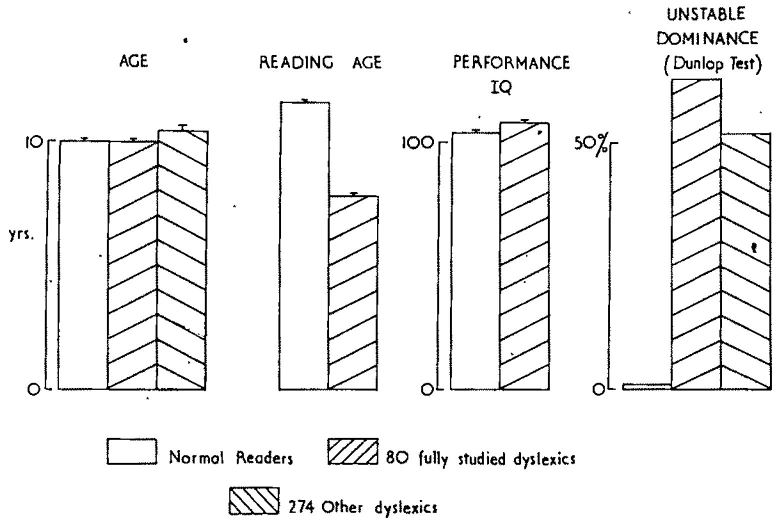

Fig. 1 *Results of studies on normal readers and dyslexic children.*

be able to identify the eye whose ocular motor and retinal signals are successfully associated (i.e., the eye contralateral to the tree that appeared to move) as the dominant one, under conditions analogous to those found when reading.

To assess the reliability of such ocular motor-retinal association the Dunlop test was repeated 10 times in each child, the slides being changed round frequently to prevent the child from guessing, but keeping the trees in the nasal field of each eye. If the test located the dominant eye on the same side 8 or more times out of 10, the subject was said to show 'fixed' or 'stable' dominance; otherwise it was termed 'unstable' or 'unfixed.' Stable dominance was said to be 'uncrossed' if the dominant eye was on the same side as the hand preferred for writing and 'crossed' if it was not. Only in a very small proportion of children could the dominant eye not be ascertained owing to lack of co-operation or suppression of the image from one eye.

Results

Fig. 1 shows some of the results of these studies. It will be noted that, while the 80 fully studied dyslexics and the 80 normal children had very similar mean ages and nonverbal IQs, the average reading age of the dyslexics was almost 4 years behind that of the controls. The mean reading age of the dyslexics was almost 10 standard errors behind that of the controls.[18]

The mothers of 116 of 354 reading-retarded children (33%) reported that theirs had been a 'difficult' birth (premature, low birth weight, excessively long or short labour, fetal distress, or other memorable obstetric problem). 124 (35%) reported a close relative (parent, grandparent, or sibling) with reading problems.

No consistent differences between dyslexic and normal children could be discerned on routine ophthalmological or orthoptic investigations apart from a slight excess of mild esophoria amongst the dyslexics. This has been found in many studies.[5] It may be taken as another sign of ocular motor immaturity. Visual acuity was usually normal and equal in both eyes. Neither amblyopia, suppression, convergence insufficiency, nor manifest squint were commoner among dyslexics.

The results of the Dunlop test were clear, however. 50 (63%) of the 80 fully studied dyslexics and 142 of the other 274 (52%) (i.e., 54% of all the children with backward reading who were examined) had failed to develop stable ocular motor dominance, whereas only one normal reader (in fact low normal) showed unstable dominance on this test. Moreover afterwards we found that, of the dyslexics whose reading errors had been assessed, all those who lacked stable dominance had been classified as 'visual.'

Crossed dominance was less than half as common in the dyslexics (18%) as in the normal children (41%), because such a high proportion of dyslexics had unstable eye dominance. Among dyslexics with stable eye dominance and normal readers crossed and uncrossed dominance was found to be almost equally common (see Orton[19] and Zangwill[20]).

Discussion

In the controlled study neither the children nor ourselves were informed which subjects were normal nor which were dyslexic, 'visual,' or 'nonvisual' until after we had tested them. Yet the Dunlop test established clearly that those whose reading problems appeared mainly visual had failed to develop stable ocular motor dominance. We conclude therefore that the test is a reliable and objective method of diagnosing 'visual' dyslexia. Since it is a test which does not involve reading itself but demands similar retinal/ocular motor associations to those required for reading, the results suggest that one of the difficulties visual dyslexics may face is a failure to develop stable ocular motor dominance. Hence they may not be able reliably to determine where the letters they see are located. Ocular motor/retinal association problems may thus help to account for perhaps half to two-thirds of cases of dyslexia.

Much evidence suggests that dyslexia sometimes results from mild birth trauma (35% of our series) or a genetic trait (33%), either of which may lead to abnormal cerebral lateralisation. Dyslexic children may lack the normal right ear advantage for comprehending verbal material in dichotic listening tests.[21 22] The difference between their right and left half fields when identifying tachistoscopically presented written material is said to be greater than normal.[23 24] They may not show the normal left half field superiority for recognition of faces,[25] and they often lack the normal right-hand advantage for dichaptic (tactile) recognition of letter shapes.[26] They may show unusual patterns of hand, foot, and eye preference.[20 26 27] The visual evoked potentials[28] and electroencephalograms[29] recorded over the left hemisphere of dyslexics may differ from those of normal controls. Among them there is even an unusually large number of right handers with anticlockwise hair whorls.[30] However, all the differences reported have been small, there is much disagreement between studies, and the most that can safely be said is that dyslexics probably do suffer mild abnormalities of cerebral lateralisation.

Our demonstration that up to two-thirds of dyslexic children fail to establish stable ocular motor dominance with respect to foveal vision is therefore not entirely unexpected. However, our results are clearer than many, and it is easy to understand how failure to develop ocular motor lateralisation may lead to inexact localisation of letters, hence difficulty with reading. We may speculate that it is this neurologically based failure of perfect association of retinal with ocular motor signals which leads to the abnormalities of dyslexics' eye movement control which are observed. The circumstances under which abnormal eye movements can be demonstrated in these patients (when they are attempting to make smooth pursuit movements, small visually triggered saccades, or fixate under visual control) all demand accurate association of retinal with ocular motor signals dealing with the central few degrees of visual angle. Thus it appears that failure to develop dependable ocular motor dominance, as revealed by repeated Dunlop testing, may confuse the ocular motor system of dyslexics at all times, not just when they are trying to read.

Our thanks are due to Mr J. McMillan under whose care these children were, and to Mr D Brownhill for much useful help and advice.

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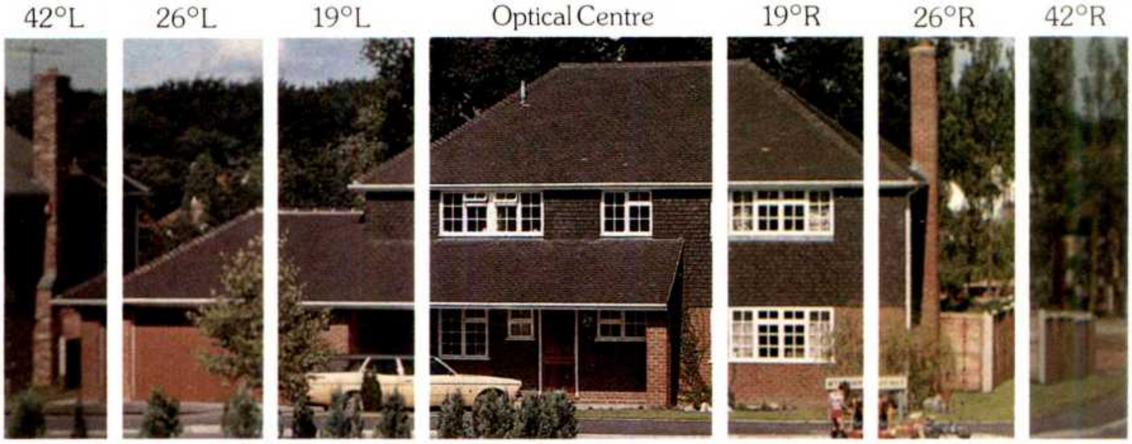

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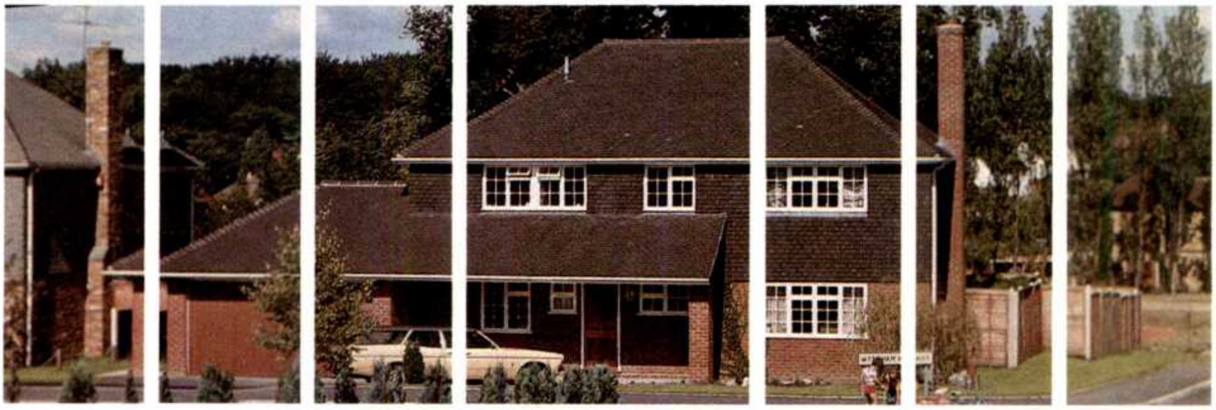

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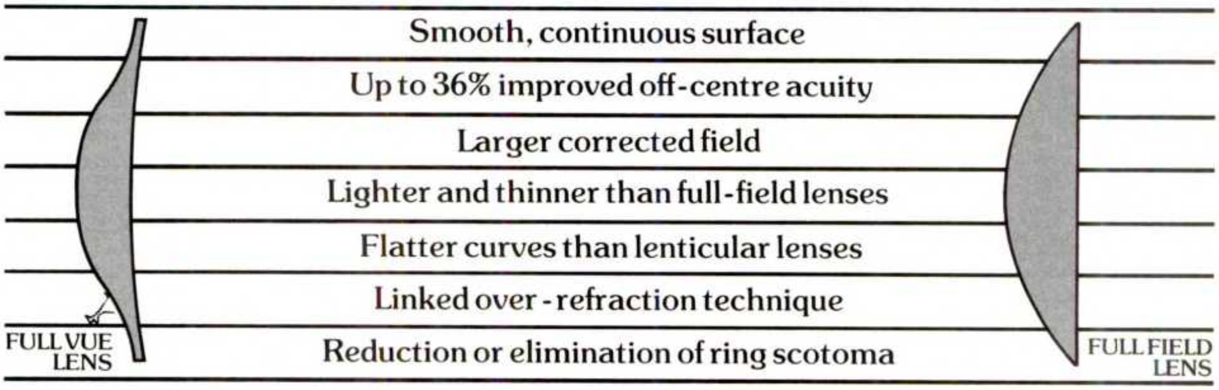

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Cryosurgery in treatment of trichiasis

SOLA MAJEKODUNMI

From the Ophthalmology Unit, Department of Surgery, Lagos University Teaching Hospital, Lagos, Nigeria

SUMMARY Ten patients with trichiasis were treated with cryosurgery by the standard retinal probe with nitrous oxide. A double freeze-thaw method was used. Nine of the patients had trachomatous trichiasis and one had conjunctival scarring. In only the latter case were the lashes destroyed, and these grew again after 2 months. Trachomatous trichiasis is frequently associated with entropion. The tarsal plate in such cases is often thickened and distorted, with extensive conjunctival scarring. The success of cryosurgical treatment of trichiasis depends not only on the type of probe used but perhaps also on the aetiology of the disease. To our knowledge no similar trial of this form of treatment of trichiasis has been carried out in eye centres in Africa south of the Sahara. Cryosurgery is simple to perform and of great potential use, particularly in areas where there is a shortage of skilled surgeons to perform the delicate eyelid operations often required in trichiasis.

The varied aetiology of trichiasis had been widely discussed.[1] In Nigeria trachoma is the commonest cause of trichiasis, and the latter, often associated with entropion, presents a major clinical problem which often results in blindness. Various treatments include epilation, electrolysis,[2] surgery,[3] and radiation.[4] Epilation is a temporary measure. Electrolysis destroys one lash root at a time[2] and has a recurrence rate of about 30% to 50%.[5] The treatment of trichiasis with surgical procedures is effective, but recurrence varies from 5% to 15%.[3]

Cryosurgery was tried after it was noticed that eyelashes were permanently destroyed in areas where cutaneous malignancy was treated with liquid nitrogen.[6] Subsequent to this observation in 1974 cryosurgery has been generally employed in some centres in the treatment of trichiasis. Sullivan *et al.*[7] and Hecht[5] in the USA using a tissue thermocouple reported 80 to 100% success rate with cryosurgery in the treatment of trichiasis. A specially designed probe and a standard retinal probe were used respectively. Collin *et al.*[8] working in the UK with cryosurgery and using standard retinal probe reported a 50% success rate in their series of 41 patients. Fifteen patients in the latter series had trachoma. Cryosurgery is simple to carry out, and depending on the size of the probe few or several adjacent follicles can be destroyed at the same time. But properly designed equipment capable of cooling the eyelash to −20°C to −30°C is required.

This paper reports on 10 patients with trichiasis treated with cryosurgery at the Lago University Teaching Hospital. The patients were followed up for 6 to 9 months.

Patients and methods

Ten adult patients, 2 males and 8 females, were treated by us at the Eye Clinic of the Lagos University Teaching Hospital. In all cases epilation of the eyelashes had been performed on several occasions by the patients themselves. Nine cases had trachoma and one other had conjunctival scarring (Table 1). In the trachoma patients the trichiasis was bilateral and involved the length of the upper lid margin, but it was localised and unilaterally involved the upper lid in the patient with conjunctival scarring. One eyelid was done at a time. The upper lid was infiltrated with 2% lignocaine (Xylocaine) with 1:100000 adrenaline and 1% amethocaine eye drops instilled into the conjunctival sac. With the Alcon retinal probe and nitrous oxide gas at pressure 560–800 pounds per square inch (39–56 kg/cm^2), the tip of the probe was placed on the conjunctival surface 2 mm from the lid margin. The

Table 1 *Causes of trichiasis in 10 patients*

Diagnosis	*No. of cases*		
	M	*F*	*Total*
Trachoma	1	8	9
Conjunctival scarring	1	0	1
Total	2	8	10

Correspondence to Sola Majekodunmi, FWACS, Ophthalmology Unit, Department of Surgery, College of Medicine, University of Lagos, PMB 12003, Lagos, Nigeria

probe was applied for 30 seconds, after which the lid was allowed to thaw. Repeated applications were made along the length of the lid margin at intervals of 2 mm. The procedure was repeated to give a double freeze-thaw method. The whole operative procedure lasted about 20 minutes in each eyelid. Chloramphenicol or gentamicin eye ointment was applied postoperatively and the eye padded and bandaged for 24 hours.

Results

Moderate to massive oedema of the eyelid with chemosis was present at the first dressing in all cases. It gradually subsided over 5–7 days. Pain was mild in all cases and usually relieved with paracetamol tablets. There was no infection, hypopigmentation, or lid necrosis. Alopecia was noticed after one week in the patient with conjunctival scarring, but the eyelashes grew again after 2 months. The eyelashes were not destroyed in any of the nine patients with trachoma.

Discussion

The effect of cold on tissues was first reported in 1665,[9] but its application to surgery (cryosurgery) was introduced in 1911 by Hall-Edwards.[10] Since then cryosurgery has been used effectively in cataract extraction and in the treatment of malignant tumours of the eyelid.[6 11–13]

The effect of low temperatures on tissues is well documented.[14–16] Various tissues react to freezing differently.[14 17] Melanocytes are noted to be more sensitive to cold than hair follicles.[5 8]

The pathophysiology of cryogenic cell necrosis has been reviewed extensively.[8 16] Rapid freezing is more destructive because of intracellular ice crystallisation. In slow freezing the cells are damaged by ice crystals formed extracellularly; they compress the cells and lead to an increase in electrolyte concentration.[16] Thawing exposes the cells to the toxic effects of electrolyte imbalance and osmotic pressure changes.

Permanent depigmentation will complicate cryosurgical treatment of trichiasis. This is a cosmetic problem in heavily pigmented races such as Nigerians. However, such patients are often unconcerned with this cosmetic problem. Hecht[5] observed alopecia postoperatively when the eyelid was frozen to −20°C. Sullivan *et al.*[7] reported that eyelids cooled to −30°C retained their general appearance and function but developed alopecia in the treated region. Both authors monitored the temperature of the eyelid with a subcutaneous thermocouple during surgery.

The failure rate in our series was high compared with others.[7 18 19] We attributed these to 3 factors. First, we used the standard retinal cryoprobe. Discouraging results have been reported with the standard retinal probe with nitrous oxide or carbon dioxide.[6 8] The main disadvantage of this probe is the small diameter of its freezing surface and the lower volume of gas flow. This also limits its usefulness in the large segment of eyelid that is often involved in trachomatous trichiasis. Good results have been reported in patients treated with specially designed nitrous oxide, gas-cooled probes.[18] Similar results have also been reported with liquid nitrogen spray.[19] But liquid nitrogen evaporates rapidly, and storage is difficult in a hot climate such as Nigeria has. Additional care is needed with liquid nitrogen to avoid damage to adjacent tissues.

The second factor accounting for the high failure rate was that the eyelid temperature was not monitored. It is possible therefore that the tissue temperature in our patients was far above −15°C to −20°C, the degree of cold said to be required to effect hypopigmentation or alopecia. Thirdly, 9 of our cases had trachomatous trichiasis. The latter is often associated with extensive conjunctival and tarsal scarring. A high proportion of patients in the series with successful results had aberrant trichiasis.[5 7] In a reported series with 50% success[8] most of the failures occurred in patients with trachoma.

The result of the treatment of trichiasis with cryosurgery should improve with the use of properly designed probes, monitoring of the tissue temperature with a thermocouple, and better selection of cases. Cryosurgery is simple to perform. In developing countries where trachoma is common and trained ophthalmologists are scarce, it is easier to train staff to carry out this technique than the surgical procedures at present available for the treatment of trichiasis.

I am grateful to Dr John H. Sullivan, Department of Ophthalmology, University of California Medical Center, San Francisco, for his useful suggestions during the preparation of this paper.

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Book reviews

Kranielle Computertomographie. Eds. M. NADJMI, U. PIEPGRAS, H. VOGELSANG. Pp. 474. DM.390·00. Georg Thieme Verlag: Stuttgart. 1981.

This very adequately illustrated synopsis of CT scanning of the head should be well received by anyone involved in the fields of radiology, ophthalmology, and neurology. The chapters systematically cover all aspects of neuroradiology and outline the clinical findings, anatomy, pathology, and so-called classical neuroradiology. They describe the findings in nuclear medicine scans, as well as arteriography and pneumoencephalography and go on to excellently illustrated CT scans. The major part that CT has to play in the diagnosis of intraorbital tumours is concisely commented on and there are a number of relevant references in this respect as well as the other topics dealt with.

I think that this book is a valuable addition to the literature on CT of the head. It is presented in an easily readable fashion in German by many well-known contributors.

I. B. NOCKLER

Professionalism and the Public Interest: Price and Quality in Optometry. By JAMES W. BEGUN. Pp. 140. £10·85. MIT Press: London. 1981.

In recent years there has been increasing criticism of the 'health care industry' with its self-regulating and self-perpetuating oligarchies, which are protected by law and justify their monopoly by demanding quality at any cost. For in the minds of many today professionalism has become a word that connotes elitism, exclusiveness, and exploitation rather than high-quality service to the consumer.

The author surveys the American scene in terms of political science, sociology, and economics, concentrating on the 'profession' of optometry, which he feels is most overtly geared to the power and profit of its members at the expense of the community.

In England we have already been alerted to the wind of change by the latest Reith lectures. And, although the pattern of professional practice is as yet less damaging to society, we are heading in the same direction, with ever increasing restrictions imposed by the oligarchies on top, which bear scant relationship to the national economy, the consumers' needs, or the freedom of the individual. The conclusions of this detailed analysis would be salutary reading for us all, and particularly for those who support the increasing powers sought by our own opticians and their jealously guarded monopoly in the sale of spectacles.

P. D. TREVOR-ROPER

Notes

Ultrasound

The ninth conference of SIDUO, the International Society for Ophthalmic Ultrasound, will be held in Leeds, England, on 20-23 July 1982. The Department of Ophthalmology of St James's University Hospital is organising a one-day teach-in on Ophthalmic Ultrasound on 19 July 1982 with an international panel of speakers. For further information contact Jeffrey S. Hillman, FRCS, Department of Ophthalmology, St James's University Hospital, Leeds LS9 7TF, England.

Visual field symposium

The Vth International Visual Field Symposium arranged by the International Perimetric Society will take place in Sacramento, California, on 20–23 October 1982. For information and registration contact Dr John L. Keltner, Department of Ophthalmology, School of Medicine, University of California, Davis, CA 95626, USA. Papers are invited and should be sent before 1 March, 1982 to Dr Anders Heijl, Department of Ophthalmology, Malmö General Hospital, S-214 01 Malmö, Sweden.

International Council of Ophthalmology

The International Council of Ophthalmology has created a secretariat, based at the Department of Ophthalmology, Beth Israel Medical Center, New York, New York 1003, USA. It carries on file information regarding the availability of temporary teaching posts for ophthalmologists in training who desire to gain experience and teaching during their training outside their own country. The information available includes: (1) institutions in different countries that are willing to accept trainees from another country for limited periods of time; (2) the individuals that should be corresponded with at these institutions; (3) the availability or nonavailability of accommodation and stipend; and (4) language, visa, and licensing requirements. Details are available on request in writing to the secretariat at the above address. The secretariat will also keep on file all information made available to it on training or teaching programmes in ophthalmology undertaken on an international level and sponsored by the International Council of Ophthalmology.

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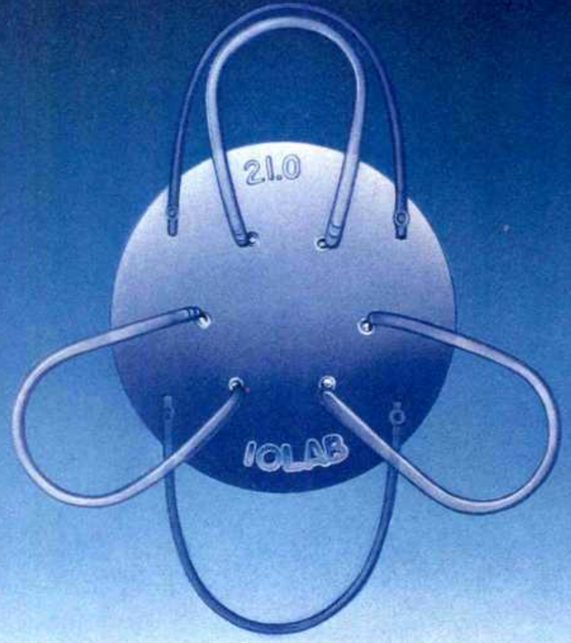

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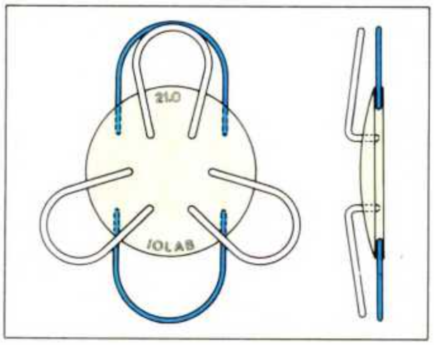

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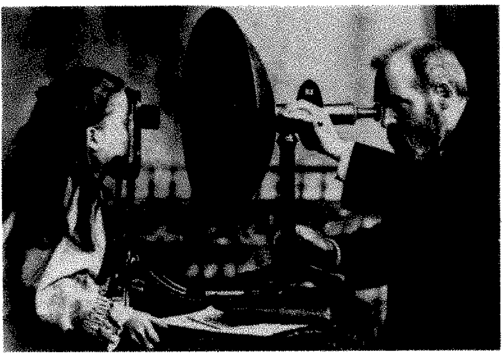

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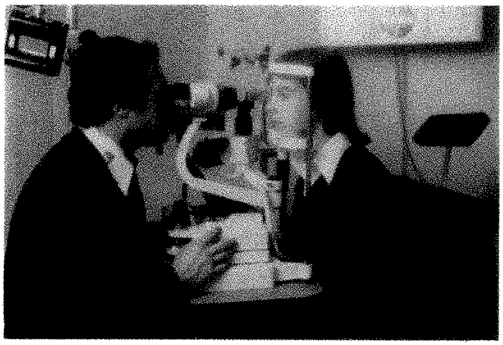

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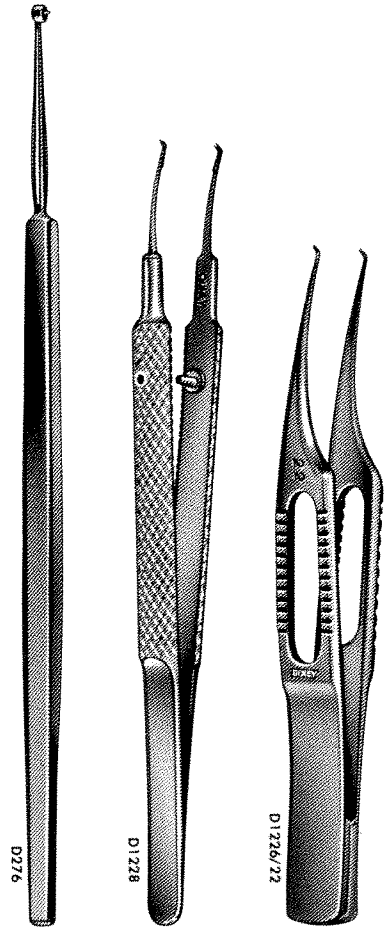

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Candidates are asked to state the extent of their experience and interest in the research aspects of surgical and medical retinal disease.

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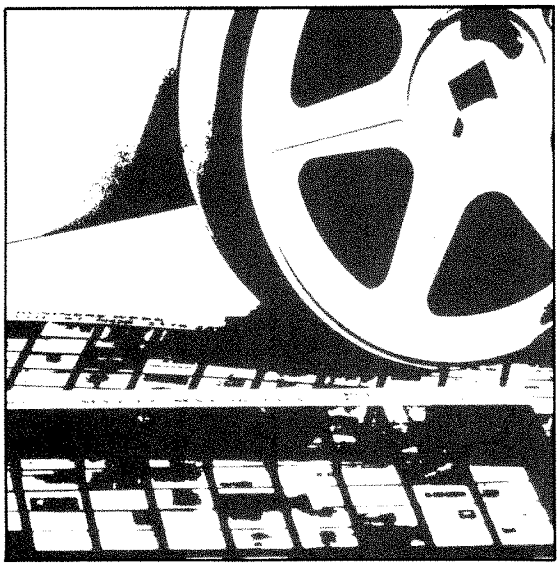

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Published by British Medical Association, Tavistock Square, London WC1H 9JR.
Typesetting by Bedford Typesetters Ltd., Bedford, England. Printed by Paramount Printing Co. Ltd., Hong Kong

British Journal of Ophthalmology May 1982 Vol. 66 No. 5

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ASTM CODEN BJOPAL 66 (5) 277-340 (1982)

ISSN 0007-1161

British Medical Association Tavistock Square London WC1H 9JR

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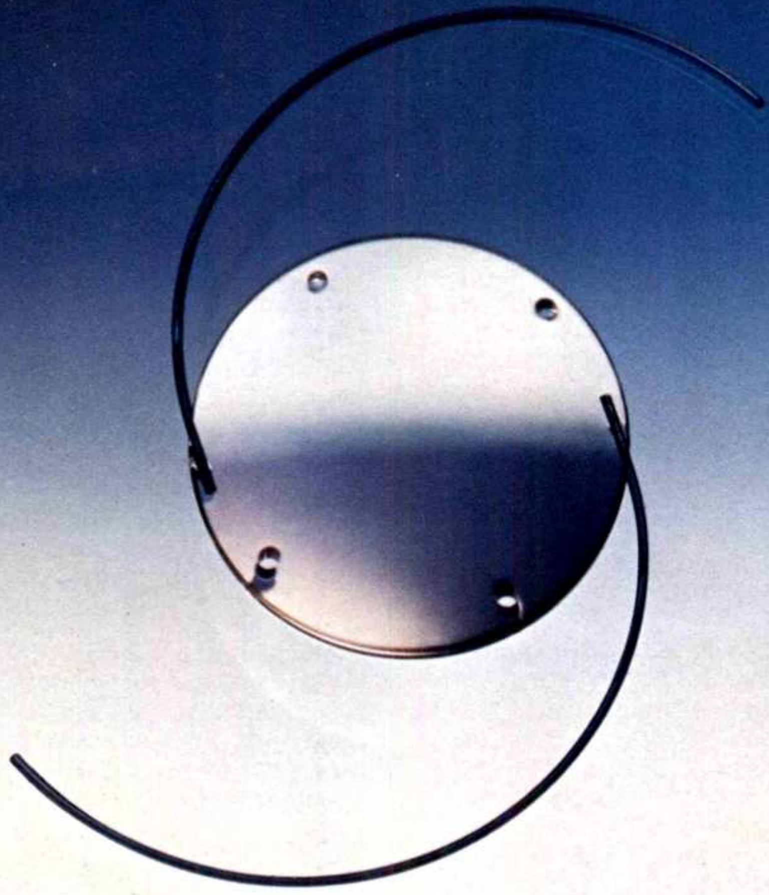

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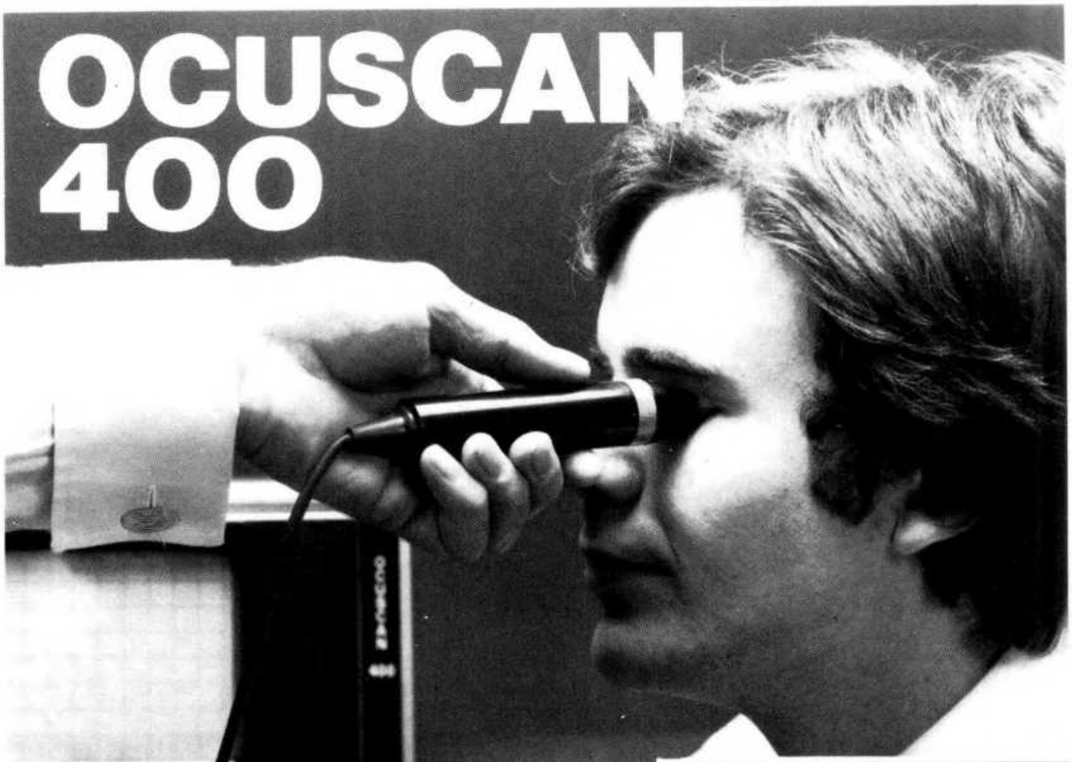

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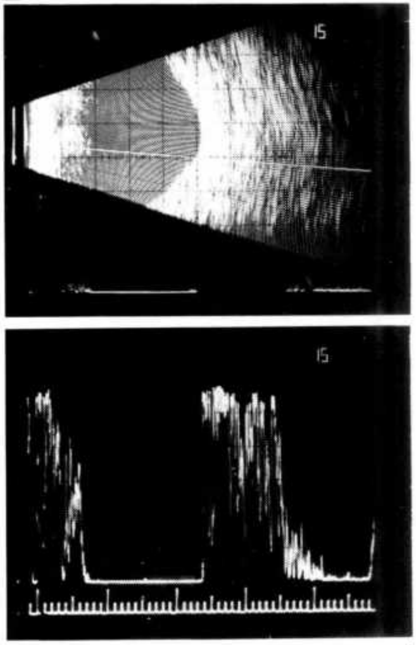

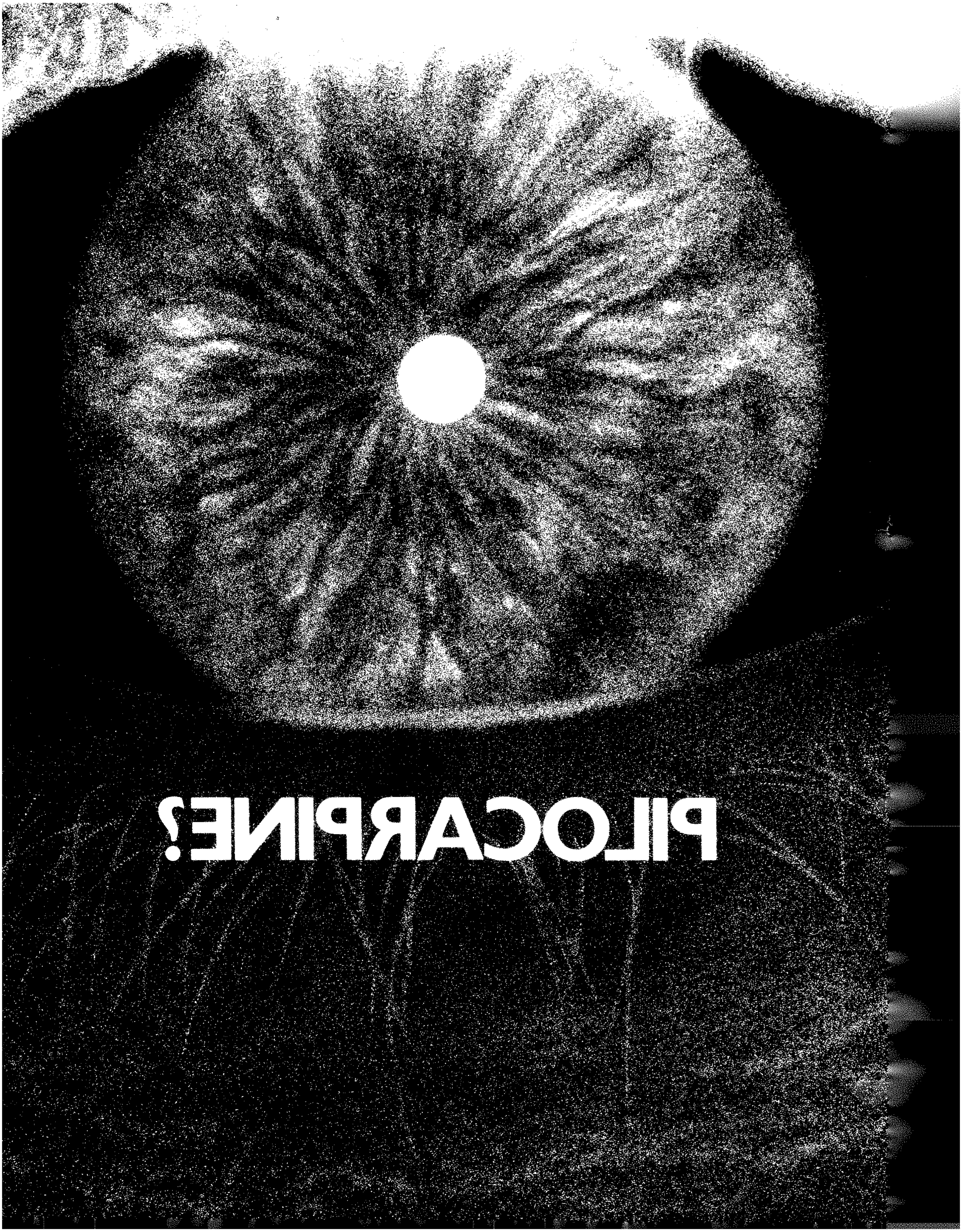
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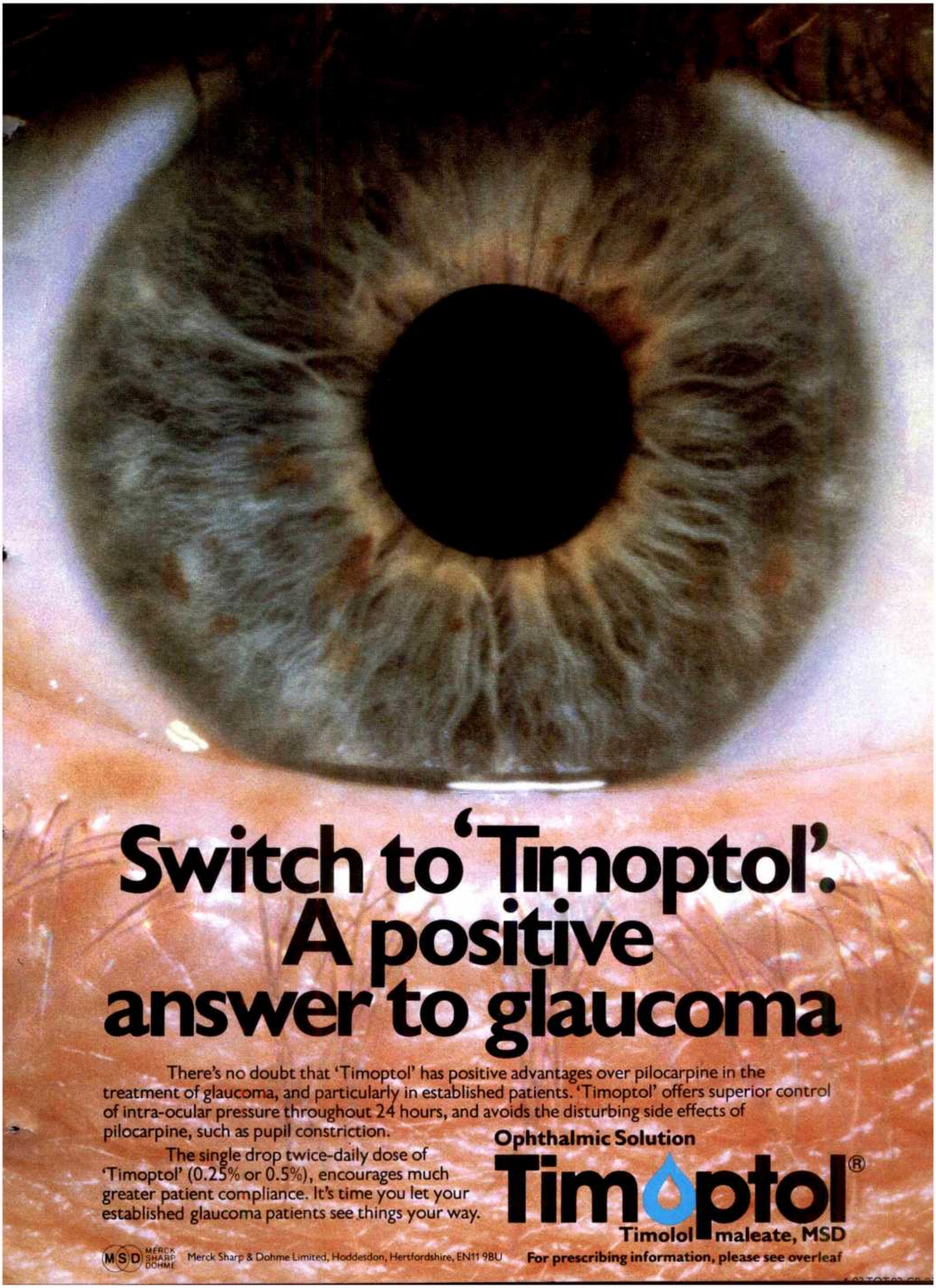

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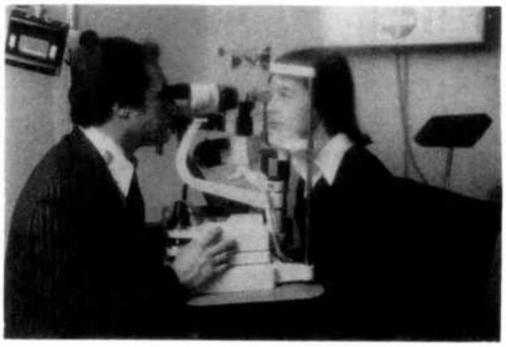

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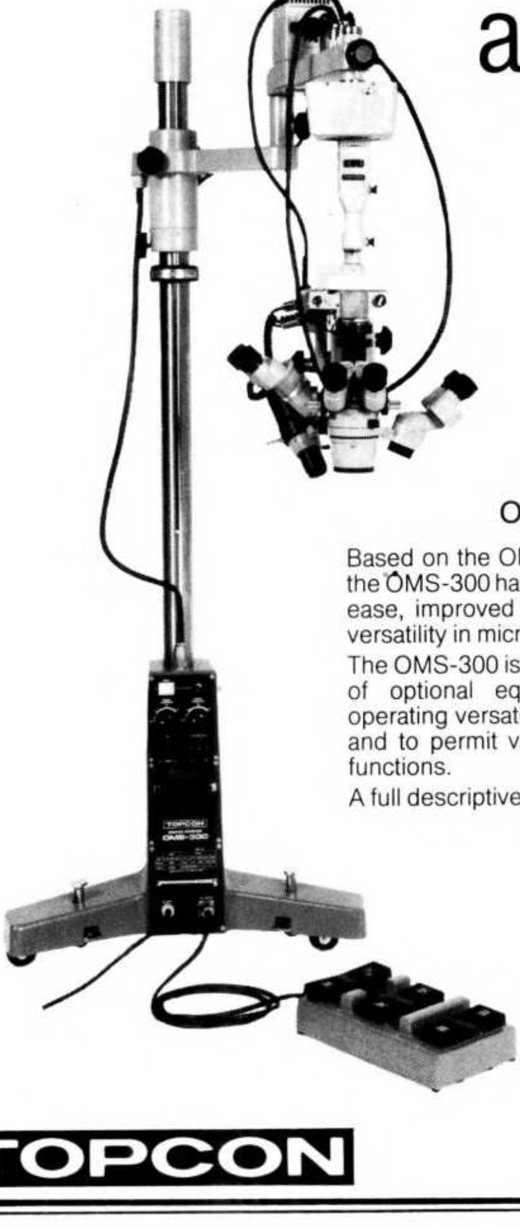

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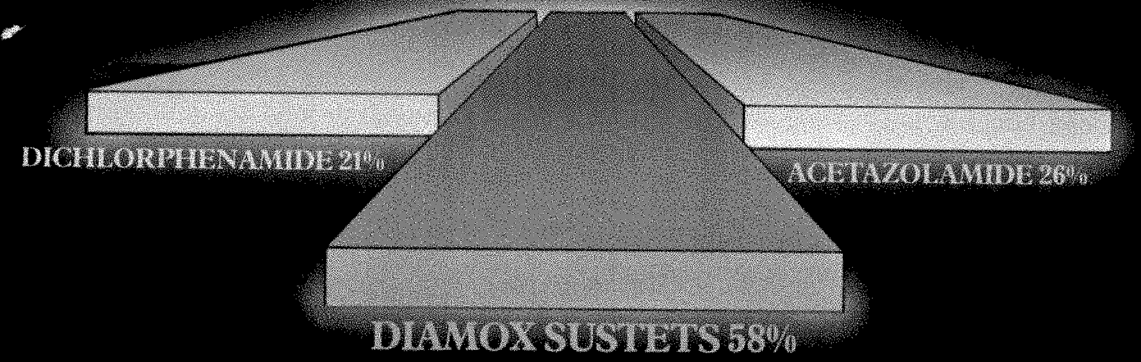

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British Journal of Ophthalmology, 1982, **66**, 341–356

Light and electron microscopy of corneal melting syndrome (Mooren's ulcer)

ROBERT D. YOUNG[1] AND PETER G. WATSON[2]

From [1]Strangeways Research Laboratory, Cambridge, and the [2]Department of Ophthalmology, Addenbrooke's Hospital, Cambridge

SUMMARY Three patients with corneal melting syndrome of Mooren are described all of whom required lamellar grafting for perforation of the cornea. All these grafts subsequently failed. Tissue excised during grafting was studied by light and electron microscopy. In all cases the conjunctiva contained large numbers of lymphocytes and plasma cells. The limbal cornea showed 3 distinct zones: the deep stroma was intact but contained a prominent macrophage infiltrate; in the mid stroma marked hyperactivity of fibroblastic cells was associated with disorganisation of the corneal lamellae; the outer stroma was heavily vascularised and infiltrated by lymphocytes and plasma cells, with destruction of the collagen matrix. At the advancing, undermined edge of the corneal ulcer the deep stroma was undisturbed, but in the superficial layers accumulation of fibroblastic cells and destruction of collagen was observed. No other cell types were found. All the failed grafts contained fibroblasts which appeared highly active, surrounded by disorganised collagen fibrils. In these patients destruction of both host and graft corneal stroma apparently resulted from the activity of fibroblastic cells.

The progressive corneal destruction described by Mooren[1] in 1867, in which the peripheral stroma is destroyed circumferentially, then centrally, with a characteristic overhanging inner edge, appears to be a distinct clinical entity. Removal of the stroma proceeds eventually to affect the entire cornea, which suffers drastic reduction in thickness (Fig. 1). Simultaneously its function becomes seriously impaired. Mooren's ulcer has been considered to exist in 2 forms, one benign, responsive to therapy, and usually found in elderly people, the other a progressive, often bilateral ulcer showing poor response to treatment and tending to occur in younger people.[2] Unfortunately many ulcers due to divergence of course or response to treatment cannot be accommodated in this convenient classification, which may generate a falsely simplified impression of a complex underlying pathology. This is underlined by the range of histopathological data obtained in several studies of this rare condition.[3–6].

The aetiology and relationship of Mooren's ulcer to systemic diseases are also poorly understood, and it has been suggested recently that the more general term 'corneal melting syndrome' would be more appropriate until this painful and destructive disorder can be more accurately characterised.[7]

In the study described here light and electron microscopy were used to examine corneal and conjunctival tissue obtained from 3 patients with

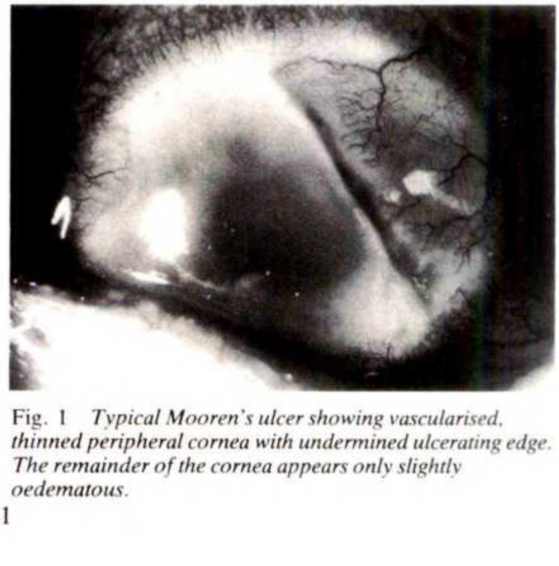

Fig. 1 *Typical Mooren's ulcer showing vascularised, thinned peripheral cornea with undermined ulcerating edge. The remainder of the cornea appears only slightly oedematous.*

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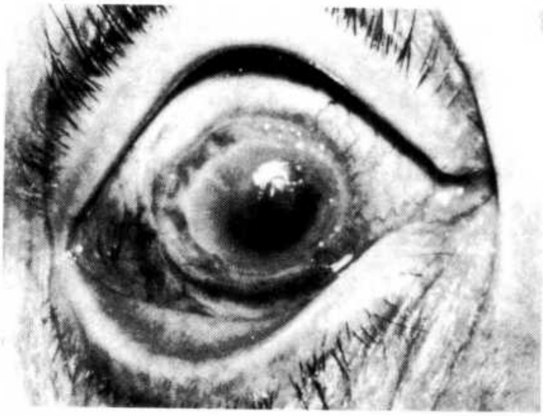

Fig. 2 *Case 1 prior to first graft (1954) with almost complete, circumferential, peripheral corneal ulceration and deeply infiltrated, vascularised, and undermined corneal edge. The lower nasal quadrant of the cornea is relatively clear.*

Mooren's disease who underwent grafting procedures. In one of these (case 3) further specimens were obtained when a second graft was performed after an interval of 10 months, thus providing an opportunity to assess the effect of grafting on the pathology of the disease. Possible mechanisms underlying the pathogenesis of Mooren's disease are discussed.

Case histories

CASE 1

This woman was first seen at the age of 43 with a history of transitory pain and redness in both eyes which settled spontaneously. One year later she suddenly developed a painful red left eye. Her vision became poor and the pain increased. She was treated for several months with a variety of drugs, including cortisone, which relieved her symptoms. The cornea showed a circumferential gutter, with oedema and diffuse infiltration of the central stroma. Some 6 months after onset the cornea became very thin 3 mm from the limbus and perforated.

Two days later the right eye, which up to this time had appeared completely normal, developed an episcleral congestion, localised between the 8 o'clock and 10 o'clock meridians, with a small deep corneal ulcer at the same site. The ulcer started at the limbus but was of maximum depth 3 mm from the limbal margin. General examination at this stage revealed nothing except a moderate hypertension (blood pressure 182/102 mmHg), an easily palpable, mobile right kidney, and advanced dental decay. She was admitted to hospital and treated with mydriatics, eye pad, and bandages, and although the perforation sealed itself the rest of the cornea began to ulcerate. Three weeks after admission there was a rapid deterioration in her vision, and the eye became very painful. It was found to be infected with *Pseudomonas pyocyanea*, which failed to respond to antibiotics. The left eye was therefore eviscerated 3 days later. At operation the whole globe was found to be infected and disorganised. Her teeth were extracted at the same time.

The peripheral corneal ulceration of the right eye extended in both directions around the limbus to affect the complete circumference within 3 months (Fig. 2). Because of increasing pain, episcleral congestion, and corneal ulceration, the entire cornea was covered with a Gunderson-type flap, which unfortunately retracted completely within 5 days.

Shortly afterwards the eye became more comfortable, but the cornea was oedematous and vascularised. Vision was reduced to counting fingers. In 1956, when the eye had been quiet for about one year, a 5 mm penetrating keratoplasty was performed. The whole thickness of the cornea was found to be oedematous, opaque, and to contain 'soft pultaceous material of questionable pathological activity.' The graft took well and remained clear during the postoperative period. She was continued on cortisone drops taken twice daily and given a course of ^{32}P B radiation therapy (400 rads), which successfully arrested the growth of fine blood vessels invading the graft in the upper nasal periphery. Graft clarity was preserved for over 12 months, when quite suddenly the epithelium became oedematous and sloughed.

On readmission for further grafting her cornea was generally cloudy, with numerous precipitates on the posterior surface. An annular lamellar keratoplasty was attempted but abandoned when the anterior chamber was penetrated. The cornea was covered with a conjunctival flap.

One month later a 9 mm lamellar keratoplasty was performed. This remained clear for about 6 months, when it was noted that the lower nasal quadrant had become 'gossamer thin' (Fig. 3). On 9 September 1960, 7 years after the onset of the condition, a total corneal graft was performed together with an iridectomy, sphincterectomy, cirumferential cyclodialysis, extracapsular cataract extraction, and anterior chamber washout. This restored the vision to 6/60 with correction. One month later the peripheral cornea again became thin and had to be resutured. It was again covered with a conjunctival flap. After this the cornea rapidly opacified, and a further full-thickness, total corneal replacement was undertaken 3 weeks later. This stayed clear for 1 week, restoring vision temporarily to 6/24, before rapidly sloughing inwards from the periphery to affect the whole

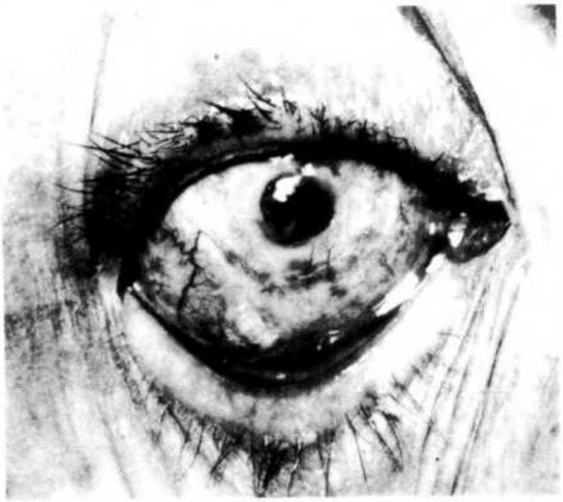

Fig. 3a

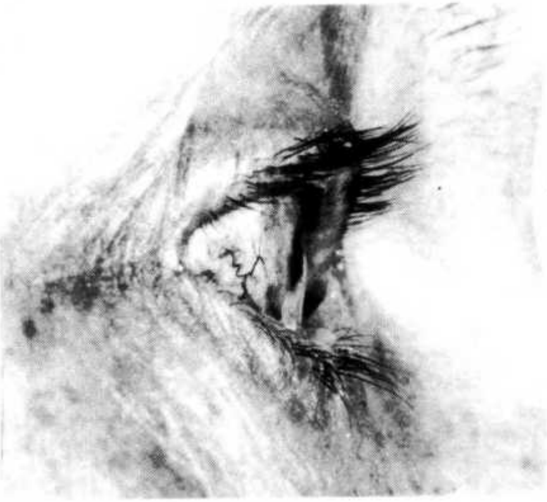

Fig. 3b

Fig. 3a, b *Case 1 after first graft (1960) demonstrates clear central transparent descemetocele following destruction of 9 mm lamellar keratoplasty.*

stroma. The small central island was removed in December 1960 and a total lamellar keratoplasty and conjunctival flap performed.

Although this conjunctival flap retracted, limited vision was possible through the thin atrophic scar for 8 years. Increased corneal scarring then made vision impossible (Fig. 4) and a further full-thickness, 7 mm keratoplasty was done with tissue-typed material. A good match was obtained. The graft remained clear for 3 days before oedema developed, and a deep gutter appeared on the host side of the graft interface. This gutter progressed over the next 3 days giving rise to 3 holes, one of which leaked. The graft was covered with conjunctiva, and, although it stopped the leakage and permitted clearing of the donor cornea, the entire periphery of the remaining host cornea became very thin.

Consequently a total anterior segment graft was performed in which remnants of the cornea, sclera, iris, and lens were removed and replaced with an intact corneoscleral segment from a size-matched donor. Excised tissues were processed for light microscopy. Within 24 hours the new anterior chamber contained aqueous and a small diffuse haemorrhage. Corneal clarity persisted but with marked folding in Descemet's membrane. The applanation pressure was 6 mmHg, with vision of counting fingers. Only a poor view could be obtained of the fundus because of the presence of an anterior vitreous membrane and thin, diffuse haemorrhages, but it appeared normal.

The eye remained quiet for 1 month, then 2 small areas of infiltrate appeared at the corneoscleral margin, which in less than one week extended over the whole limbal cornea. She had been given 30 mg prednisolone from the time of the operation, and to this was added 300 mg azothioprine, reducing to 150 mg per day. There was no further extension of the ulcer for one month, when the whole peripheral cornea became densely infiltrated, followed by the central corneal stroma over the next 6 months (Fig. 5). This corneal tissue was spontaneously removed, and a thin atrophic scar was left. No further surgery was attempted before the patient's death from pneumococcal pneumonia at the age of 66 in 1975.

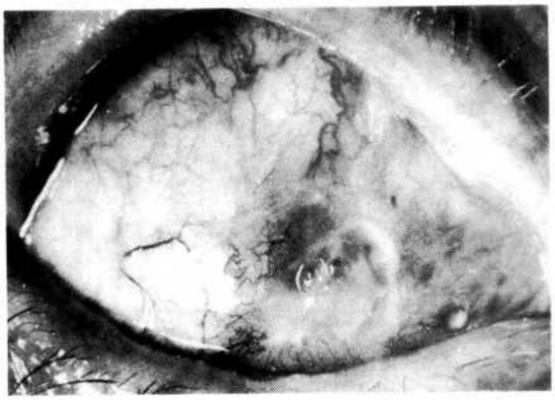

Fig. 4 *Case 1 after fifth graft (1968). Fibrosis of the thin atrophic scar through which she had seen for 8 years.*

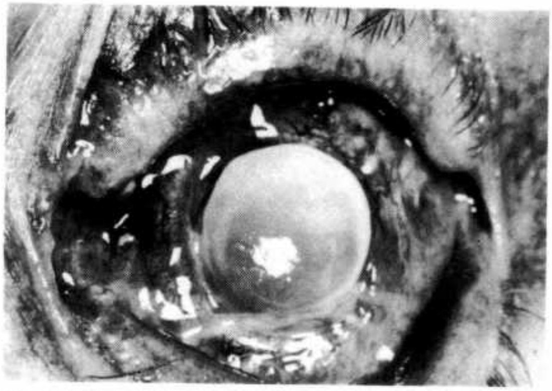

Fig. 5 *Case 1 (1969). Appearance following total anterior segment graft showing ulceration of donor cornea with donor sclera uninvolved. Corneal destruction resembles typical Mooren's ulceration in ungrafted corneas.*

CASE 2

In July 1973 this 58-year-old woman suddenly developed severe pain, associated with photophobia and watering, in her right eye. There was no history of injury or of other systemic disorders. Within one week the left eye became red but was not as painful as the right. Both corneas were oedematous when first seen, and there was a small guttered ulcer adjacent to the limbus of her right eye. Both eyes were treated with an intensive course of steroid eye drops which resolved the pain, corneal oedema, and inflammation, though both corneas remained scarred.

About 12 months later both eyes became extremely painful, and she presented with the same corneal appearance. This time, however, discomfort was not reduced by a course of local steroids. Vision gradually failed to hand movements in the left eye, and there was a progressive loss of tissue in the lower half of the left cornea (Fig. 6). The right eye became quiescent, and, although very thin, the corneal scar remained strong and inflammation slowly cleared (Fig. 7).

In July 1977 vision suddenly deteriorated in the left eye, and the thinned cornea perforated. She was admitted to hospital and a 9 mm lamellar keratoplasty was performed. All necrotic corneal tissue was removed to the level of Descemet's membrane and the donor cornea sutured into this bed. No attempt was otherwise made to seal the perforation. The graft cleared normally, although for a period 2 anterior chambers were detectable below the graft centre.

After 3 months this graft suddenly became oedematous, but there was no apparent destructive change in the cornea until June 1978, 10 months after grafting. Then the eye became red and painful, and a peripheral corneal gutter appeared in the donor tissue. She was readmitted to hospital, and a 6 mm penetrating keratoplasty was placed through the old graft. The cataractous lens was also removed in addition to some adhesions of the iris to the old perforation site. The excised corneal button was taken for microscopy.

After the graft the previous limbal inflammation and guttering resolved, and graft clarity persisted for one month. Then the first donor lamellar graft became swollen from 6 to 4 o'clock below, but the central corneal button remained entirely clear.

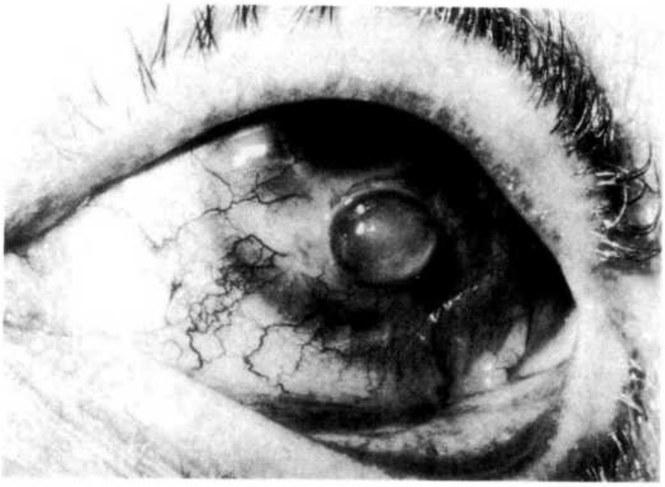

Fig. 6a

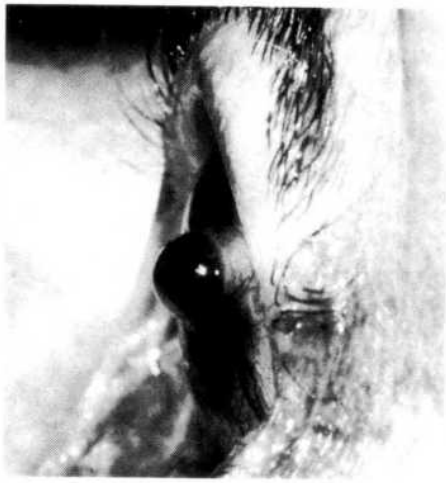

Fig. 6b

Fig. 6a, b *Case 2 showing left eye at presentation. Descemetocele formation in previously ulcerating cornea. The cornea is transparent and undamaged superiorly.*

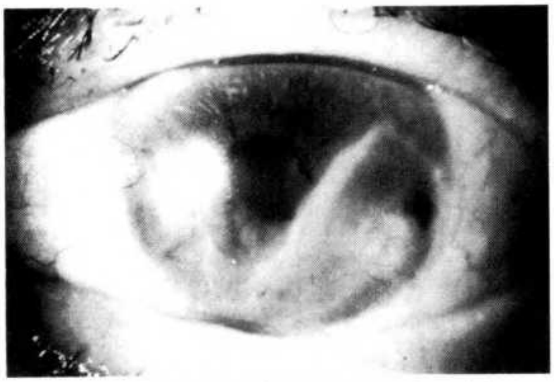

Fig. 7 *Case 2 showing right eye at presentation. Quiescent, spontaneously healed, thinned peripheral cornea with anterior synechiae formation at 8 and 4 o'clock.*

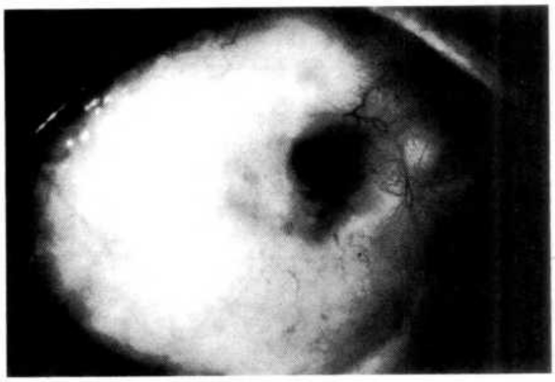

Fig. 8 *Case 3 prior to first graft. The cornea is opaque and heavily vascularised with descemetocele formation at 2 o'clock.*

However, one month later, in January 1979, a gutter advanced between 2 and 4 o'clock in the central penetrating graft. This rapidly extended centrally, but was successfully arrested by an intensive course of local and systemic steroids and the application of a soft contact lens. This restored her vision to 6/36. The rest of the cornea remained clear for a further year, when it became opaque. However, there have been no more episodes of destructive corneal changes. The right eye has remained quiescent throughout this period.

CASE 3

In June 1973 this 57-year-old woman injured her left eye while working at a threshing machine. This did not require any immediate treatment, but 5 days later she suddenly developed severe pain in this eye. She consulted her doctor, who treated her for 2 weeks with hydrocortisone drops. As there was no improvement in the eye, she was referred to hospital and was immediately admitted.

At this time the right eye was completely normal, with a vision of 6/6. The left vision was reduced to 6/36, and a deep undermined corneal ulcer was noted involving the whole of the nasal margin and extending to the 2 o'clock meridian on the temporal side. The conjunctiva was congested in the region of ulceration but not elsewhere. A complete tarsorrhaphy was undertaken in 2 stages in order to cover the cornea completely. In spite of this the pain persisted, and during the succeeding month the cornea swelled and became completely opaque. Over a period of 2 years the cornea vascularised, the eye became phthisical, and vision was lost.

Five years later, in June 1978, she had a sudden onset of pain in her right eye. She was readmitted to hospital where the vision was found to be 6/18 in the right eye and no perception of light in the left eye. The right cornea was completely oedematous and only semi-transparent. In the 3 and 9 o'clock meridians there were deep, limbal corneal ulcers with associated stromal infiltration to the depth of Descemet's membrane. The infiltration continued to a lesser extent adjacent to the limbus throughout the whole circumference of the globe.

In July 1978 the limbal conjunctival tissue was excised. This resulted in healing of the corneal ulcers, a diminution of the corneal oedema, and some reduction in infiltration and injection of the eye. She was discharged, but within one week the pain had returned, and on readmission vision had fallen to 6/60 and the ulcers were found to have recurred. On this occasion the left eye was removed and the right cornea was covered with a Gunderson flap, which adhered to the ulcerated areas to leave a central clear zone, giving reasonable vision of 6/36.

The situation remained almost static for 12 months, when the ulcer recurred. The vision was found to be 2/60, with the cornea opaque and vascularised. Vascularisation was largely superficial and most apparent in areas adjacent to the ulcers. A further conjunctival excision was performed, but there was no improvement in the vision or in the appearance of the eye.

When we first saw the patient in October 1980 the visual acuity was hand movements only in her right eye. The cornea was thin and heavily vascularised from 11 o'clock, around the entire lower half, to 2 o'clock on the nasal side. The upper wedge of cornea was free of vessels, although opaque, and there was a Descemetocele in the upper temporal quadrant (Fig. 8).

Investigation revealed a polyclonal increase in IgG to 15·5 g/l (normal 7–13); however, conjunctival

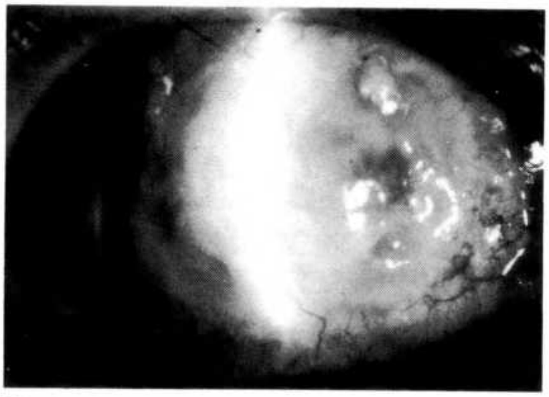

Fig. 9 *Case 3 prior to second graft. Original 9 mm lamellar graft has been destroyed leaving a very thin, opaque cornea.*

biopsy revealed no positive immunofluorescence staining for IgG, but it did induce blast cell transformation when cultured with the patient's lymphocytes. All other investigations, including ultrasonography of the posterior segment, were normal.

In October 1980 a 9 mm lamellar keratoplasty was performed in which the stroma was removed to Descemet's membrane throughout the whole area. Excised tissue was used for immunological and histological studies. The site thus prepared was covered with a 0·5×9 mm lamellar graft of fresh donor material from a 20-year-old man. Postoperative treatment was with antibiotic and prednisolone drops every 2 hours. The graft remained entirely clear for 3 weeks and vision returned to 6/36. At about this time the corneal epithelium and underlying stroma became slightly oedematous and thin, and then in early December, 8 weeks after the operation, a gutter developed in the graft between 4 and 8 o'clock. This rapidly extended, and within 2 weeks there was a crescentic defect involving a quarter of the graft. The advancing edge of the ulcer had a thickened, undermined edge. She was, however, able to see

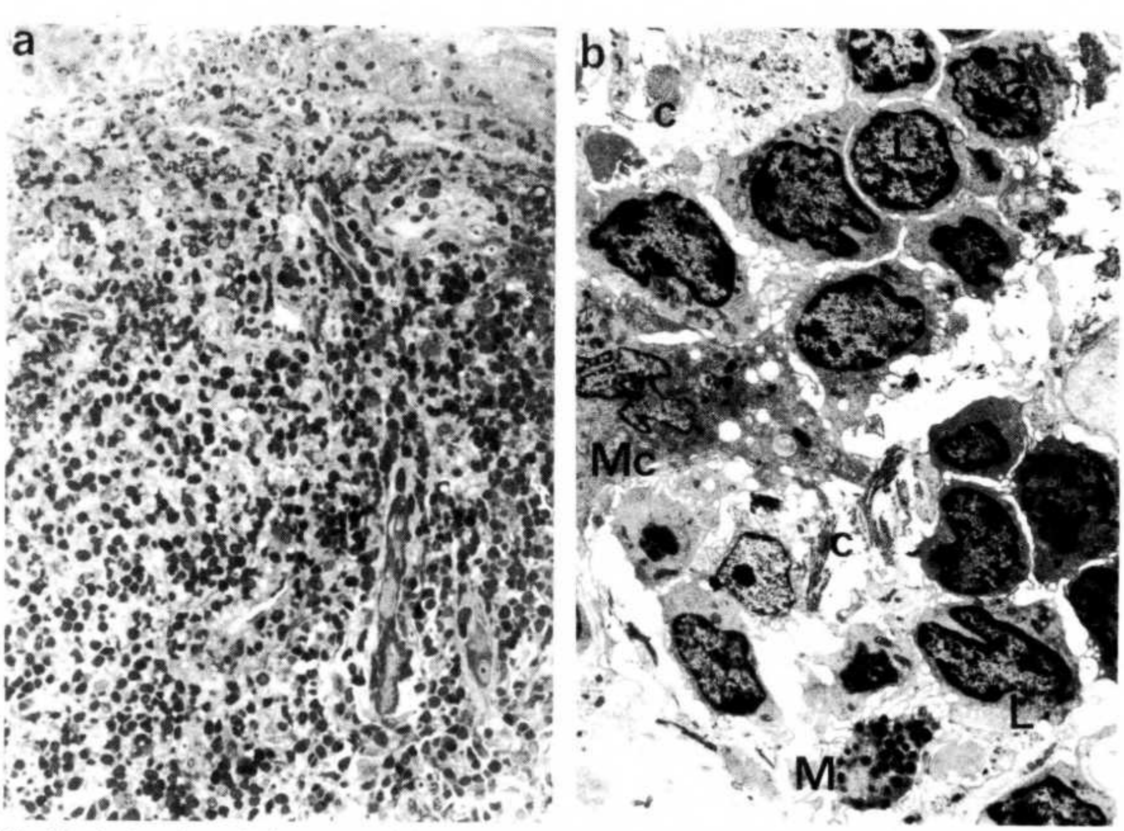

Fig. 10 *Conjunctiva.* a. *Light micrograph showing intact conjunctival epithelium and cellular infiltration of underlying stroma. (×192).* b. *Electron micrograph illustrates dense clustering of stromal lymphocytes (L), a mast cell (M), macrophage (Mc), and collagen fibrils (c). (×3,400).*

adequately for 6 months, at which point she ran out of medication. As soon as this was discontinued, pain recurred and her vision deteriorated. Itching, redness, and discomfort persisted until she was restarted on medication some 3 months later. By this time the whole of the graft was removed except for a very thin deep lamella (Fig. 9). In August 1981 a further 11 mm lamellar keratoplasty and limbal conjunctival excision was performed in a similar manner to the original graft. The donor was a 59-year-old female. Excised tissue was again taken for microscopy.

Postoperatively she has been treated with prednisolone and azothioprine, and apart from a few epithelial bullae the graft has remained clear. Immunofluorescence staining for IgG in conjunctiva and cornea has again been negative.

Methods

In Case 1 the excised anterior segment was fixed in buffered formalin and embedded in paraffin wax. Sections were stained in haematoxylin and eosin.

Tissue excised from cases 2 and 3 was fixed for 2 hours at room temperature in 2·5% glutaraldehyde, buffered to pH 7·2 with 0·1 M sodium cacodylate containing 3 mM $CaCl_2$. After washing in buffer at 4°C it was postfixed in buffered 1% osmium tetroxide for 1·5 hours at room temperature, dehydrated in ethyl alcohol, cleared in propylene oxide, and embedded in Araldite.

Thick sections (approximately 1 μm) were stained in 1% toluidine blue in 1% aqueous borax solution and used for light microscopy and orientation for ultramicrotomy.

Thin sections (approximately 700 nm) were stained in alcoholic uranyl acetate and lead citrate and examined in an AEI EM6B or Philips 201C electron microscope.

Observations

CONJUNCTIVA

Specimens removed from all 3 cases revealed a normal intact epithelium and basement membrane, overlying a slightly swollen hyperaemic stroma which contained dramatic numbers of small lymphocytes (Fig. 10). These cells formed dense clusters, filling the subepithelial palisades of Vogt and extending deeper into the stroma. Some showed signs of necrosis. Smaller numbers of stromal plasma cells and scattered mast cells, most undergoing degranulation, were also identified in addition to native conjunctival fibroblasts and macrophages.

LIMBAL CORNEA

The limbus adjacent to the ulcer was examined only in case 3, where an apparent stratified organisation was discovered (Fig. 11). This comprised an outer, necrotic, heavily vascularised 'pannus,' infiltrated with lymphocytes and plasma cells, an underlying zone with many attenuated cells, and deep to this a narrow band of large, densely staining irregular cells.

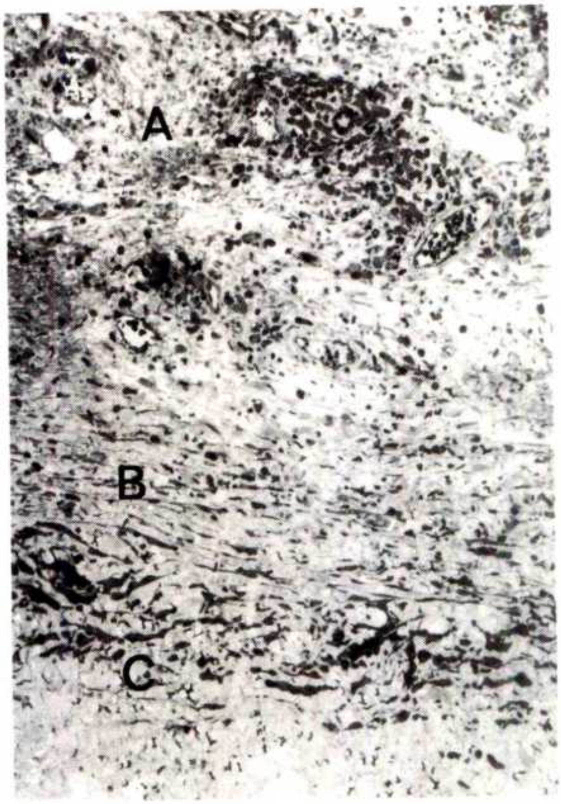

Fig. 11 *Limbal cornea. A stratified organisation of the stroma is evident at this site comprising:* A. *a superficial stromal 'pannus' with perivascular accumulation of lymphocytes and plasma cells;* B. *an intact mid stromal zone containing attenuated fibroblastic cells;* C. *a deep stromal macrophage infiltrate.* (×*145*).

Few viable fibroblasts could be located in the outer ulcerated stroma. In contrast, plasma cells and small lymphocytes were relatively numerous (Fig. 12), especially in the vicinity of superficial blood capillaries. Extravascular red blood corpuscles were a common feature at this level. Mast cells were less frequently observed than in conjunctival tissue. The collagenous component of the distal stromal matrix exhibited an advanced state of destruction, with large tracts of necrotic stroma occupied by pycnotic cells and accumulations of extracellular organelles and membraneous structures. Various types of cytoplasmic granules were present free in the matrix,

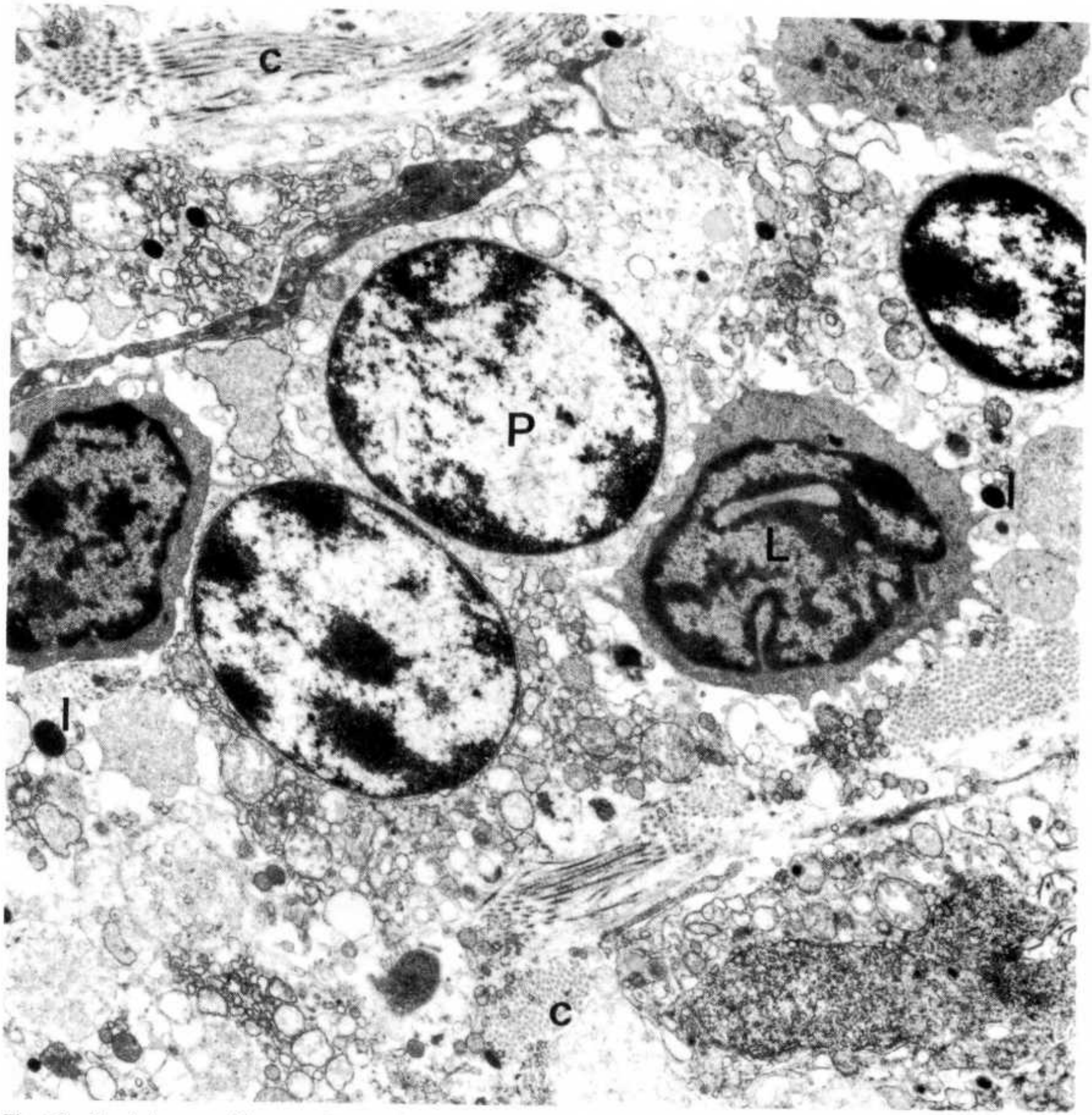

Fig. 12 *Limbal cornea. Electron micrograph of superficial stroma showing lymphocytes (L) and degeneration of plasma cells (P). Cellular debris, including organelles and lysosomal granules (l) is abundant, but relatively few intact collagen fibrils (c) are present. (×7800).*

including lysosomal and mast cell granules (Figs. 12 and 13). The abundance of extracellular rough-surfaced endoplasmic reticulum (RER) and plasma cells in various stages of necrosis suggested that these cells made a major contribution to the high level of cell debris present (Fig. 12). Intact collagen fibrils were rarely seen in the superficial stroma, where they had largely been replaced with a diffuse amorphous or fine fibrillar substance (Fig. 13). Relatively few polymorphonuclear (PMN) leucocytes were located. These cells showed little evidence of phagocytosis of the abundant extracellular material available (Fig. 13). Observations of vascular tissue at the limbus suggested a high level of reorganisation, with small-vessel occlusion, destruction, and formation ensuing simultaneously (Fig. 14). New vessels were identified

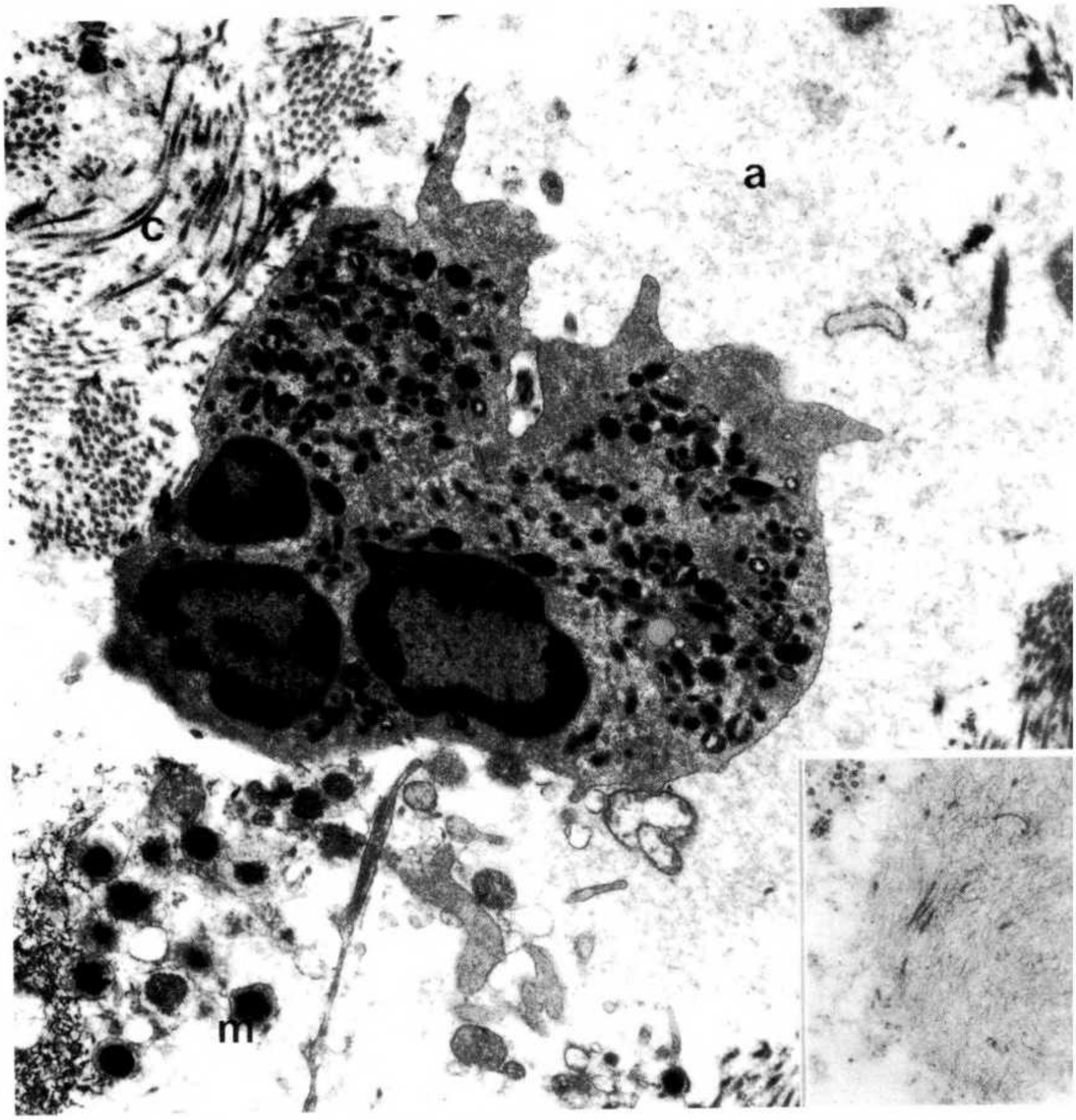

Fig. 13 *Limbal cornea. A PMN leucocyte in superficial stroma shows little evidence of phagocytosis. The surrounding matrix contains extracellular mast cell granules (m) and some intact collagen fibrils (c). (×11 700). Elsewhere a diffuse amorphous substance (a), or a fine fibrillar material (inset ×18 200) is present.*

as those of small diameter with bulky endothelial cells, surrounded by masses of basal lamina material and large attendant pericytes. Such vessels were commonly located at sites distal to the ulcer, while more centrally, towards actively ulcerating cornea, small vessels were frequently found with necrotic endothelium or completely ruptured walls (Fig. 14b).

Deeper in the limbal stroma (Fig. 11B) flammatory leucocytes were scarce and the c nective tissue matrix showed less advan destructive changes. Here numerous fibrobl containing prominent Golgi regions, mitochond and RER were present (Fig. 15). These cells w densely packed and displayed an increa cytoplasm:nucleus ratio over normal, corneolin fibroblasts. An impression gained from thick sections of an unaltered lamellar organisation in the mid stroma was not confirmed at higher magnification, whereupon it appeared markedly oedematous. Disorganisation of collagen fibrils and wide variation in interfibrillar distance were characteristic. In addition electron-dense cross-banded material and sprays of microfibrils, formed by the dissociation of individual collagen fibrils, were commonplace. Occasionally sections through stromal fibroblasts revealed collagen fibrils apparently contained within cytoplasmic vacuoles (Fig. 15b, c).

A band of large, irregular cells situated deep in excised limbal tissue was shown by electron microscopy to consist primarily of macrophages (Figs. 11C and 16). These contained extensive Golgi complexes and numerous elongate mitochondria. Intracytoplasmic granules were also numerous. Peripherally the macrophage cell membranes were often thrown into an elaborate veil of slender pseudopodia which surrounded individual cells and projected into the matrix (Fig. 16). Fibroblasts and lymphocytes were sometimes seen in close contact with macrophage veils. Disruption of stromal lamellae at this level resembled that described previously, except that here individual collagen fibrils retained their structural integrity.

CORNEAL ULCER

All 3 cases illustrated a typical thickening of epithelium immediately adjacent to the ulcer on its central edge (Fig. 17a). The corneal stroma which was denuded of epithelium overlying the ulcer was elsewhere surfaced with epithelial cells of normal thickness and structure. Bowman's layer was broken and distorted (case 3) or absent (cases 1 and 2) from the nonepithelialised portion of the ulcer and appeared sunken into subjacent necrotic stroma (Fig. 17b). There was no major accumulation of infiltrating leucocytes associated with the ulcerating corneal stroma. In case 1 polymorphonuclear leucocytes were scattered diffusely throughout the corneal stroma, both around the ulcer and in nonulcerating tissue. In contrast, hypercellularity of the superficial stroma in cases 2 and 3 resulted from a concentration of fibroblastic cells and the reduction in thickness of lamellae

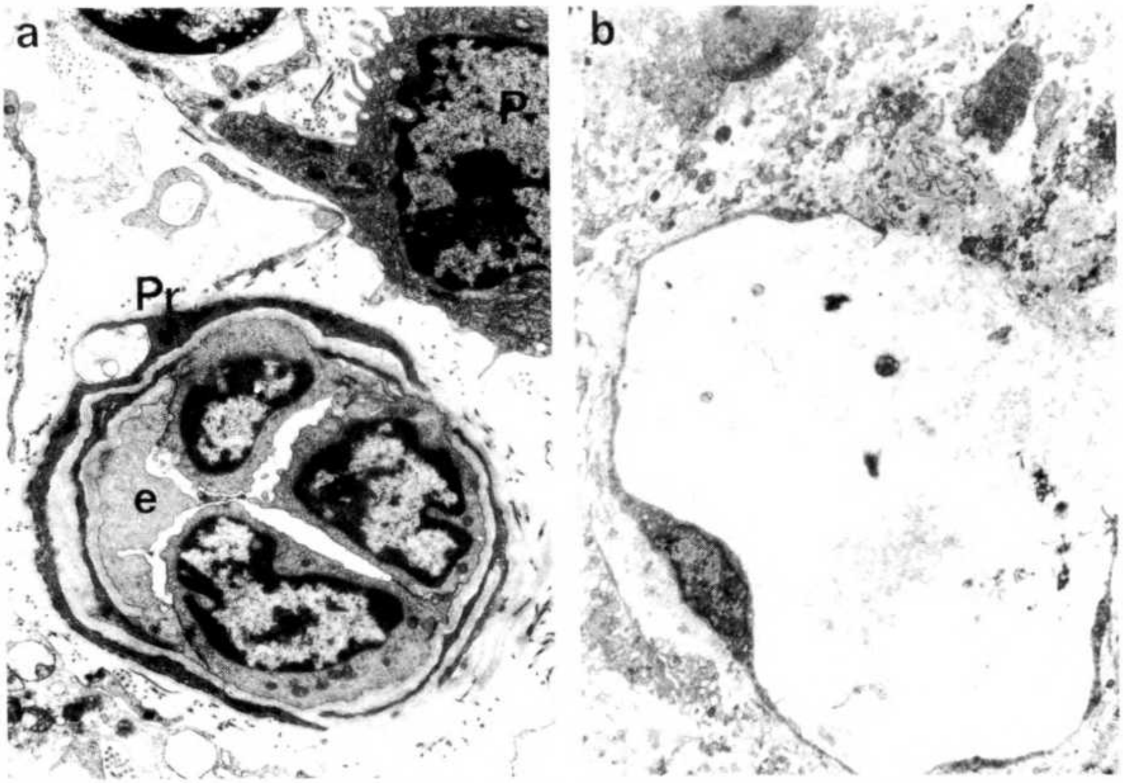

Fig. 14 *Limbal cornea.* a. *Occlusion of a small capillary in superficial stroma; endothelial cells (e), pericytes (Pr) and plasma cell (P). (×3800).* b. *Capillary destruction in superficial stroma adjacent to corneal ulcer. (×13 500).*

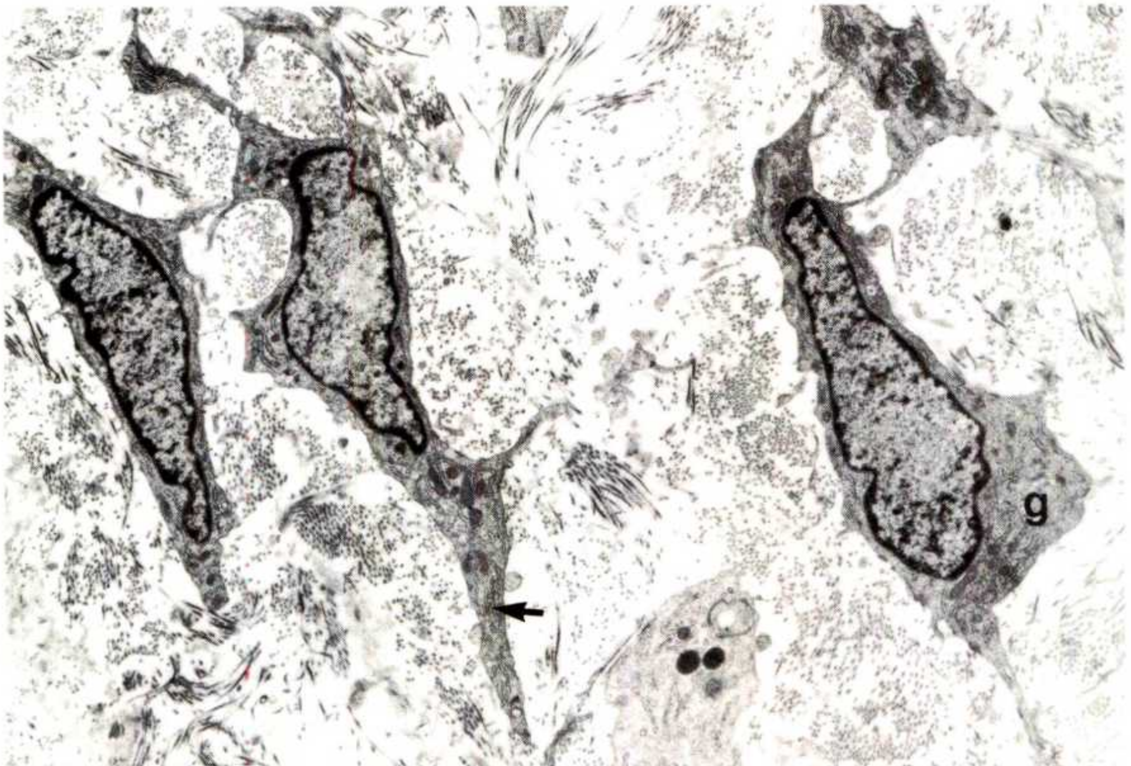

Fig. 15 *Limbal cornea.* a. *Electron micrograph of mid stroma showing disorganisation of lamellae and presence of 'active' fibroblasts with prominent Golgi (g), RER (arrow) and mitochondria. (×6600).* b. *Mid stromal collagen fibrils appear dispersed into component microfibrils (arrows) (×45 000) or* c. *contained within intracellular vacuoles. (×30 000).*

(Fig. 17c). These cells showed varying stages of necrosis, including nuclear karyorrhexis and the development of autophagic vacuoles. Necrotic cells filled the upper stroma at the ulcer centre and peripherally around the fractured Bowman's layer in case 3. Specimens removed from cases 2 and 3 at regrafting showed cells of identical structure and organisation, lending a similar level of hypercellularity to the host corneal tissue where it apposed the margins of the graft. Although dissociation and apparent phagocytosis of stromal collagen fibrils, as recorded at the limbus, were present here also, the

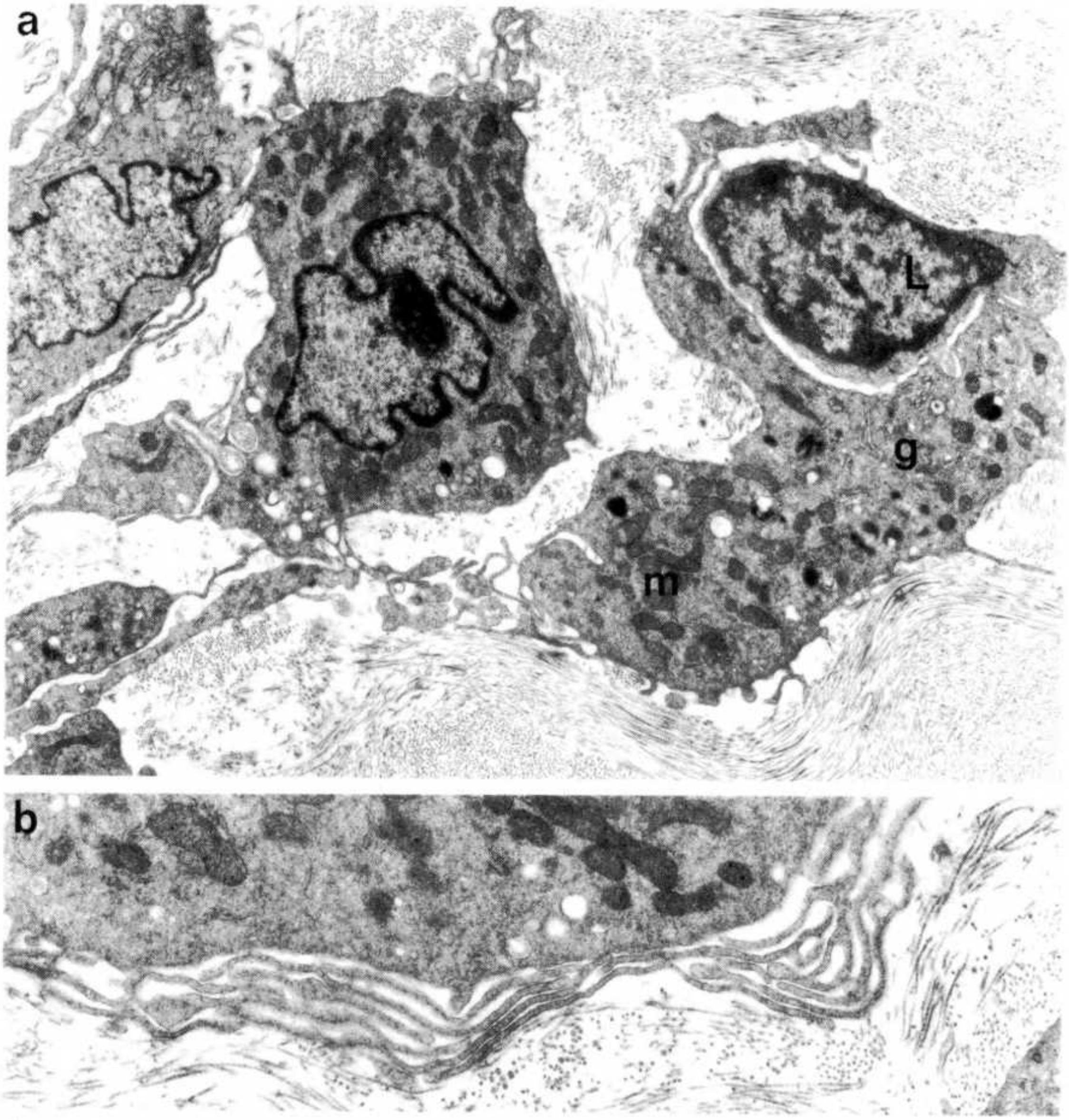

Fig. 16 *Limbal cornea.* a. *A macrophage in the deep stroma, in close contact with a small lymphocyte (L), contains an extensive Golgi complex (g) and numerous mitochondria (m). (×7500).* b. *Veil-like extensions of a macrophage cell membrane. (×13 500).*

architecture of the deep stroma was relatively undisturbed.

GRAFT STRUCTURE

Observations of tissue from failed lamellar grafts were made in cases 2 and 3 at 13 and 10 months respectively following implantation. In general, preservation of epithelium, basement membrane, and Bowman's layer at the graft centre was excellent, but with an irregular surface contour in case 3. In both cases graft stroma showed some heterogeneity, with zones of localised oedema causing both loss of lamellar organisation and disorganisation of collagen fibrils. In addition graft fibroblasts displayed several

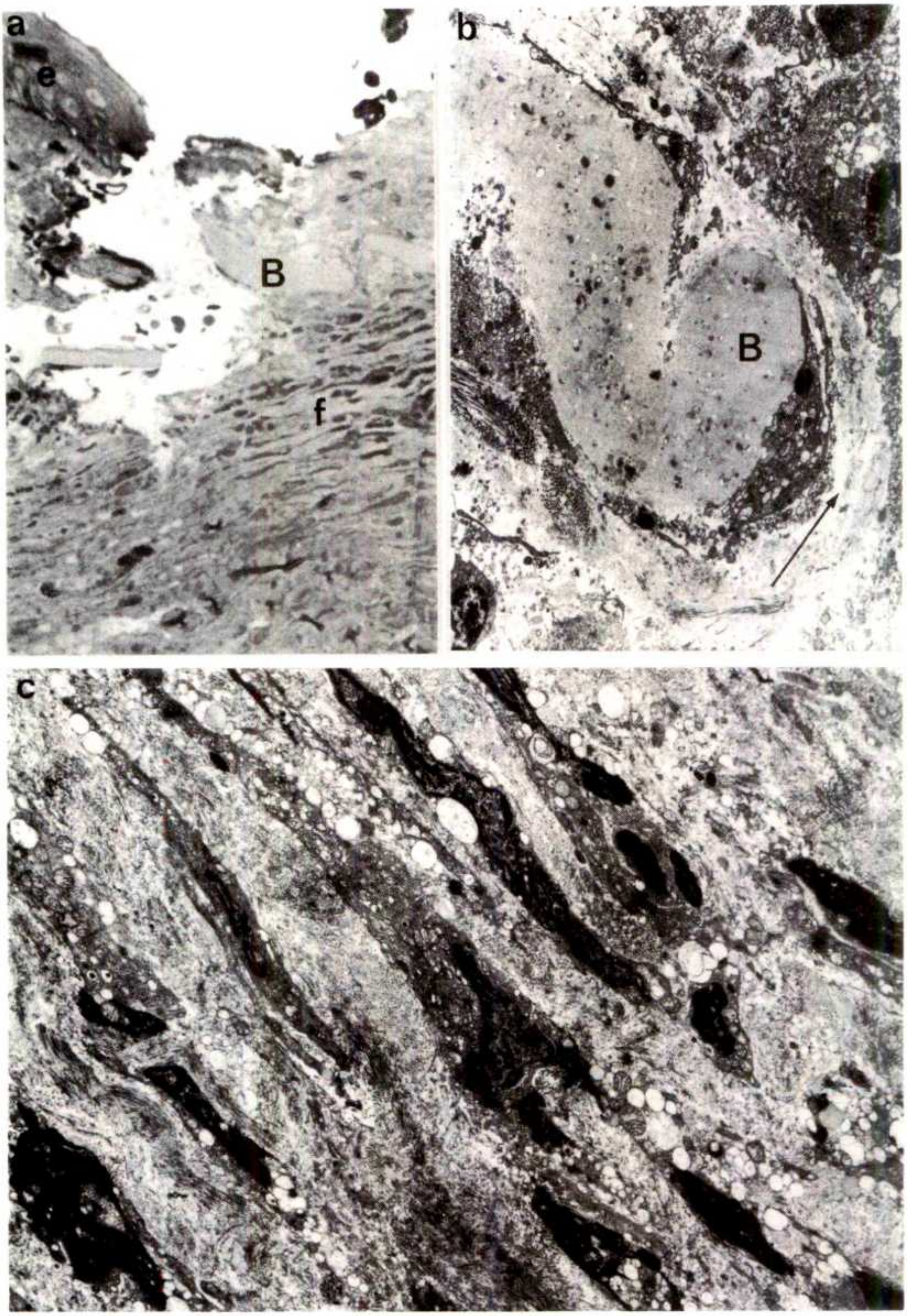

Fig. 17 *Corneal ulcer.* a. *Light micrograph of corneal ulcer in case 3 showing thickened epithelium (e), fractured Bowman's layer (B), and concentration of fibroblastic cells in superficial stroma (f). (×374).* b. *Fractured Bowman's layer (B) is distorted and sunken into the underlying ulcerating stroma. Arrow indicates direction of corneal surface. (×8000).* c. *Electron micrograph showing concentration of necrotic fibroblastic cells and reduction in superficial lamellae at ulcer site. (×5200).*

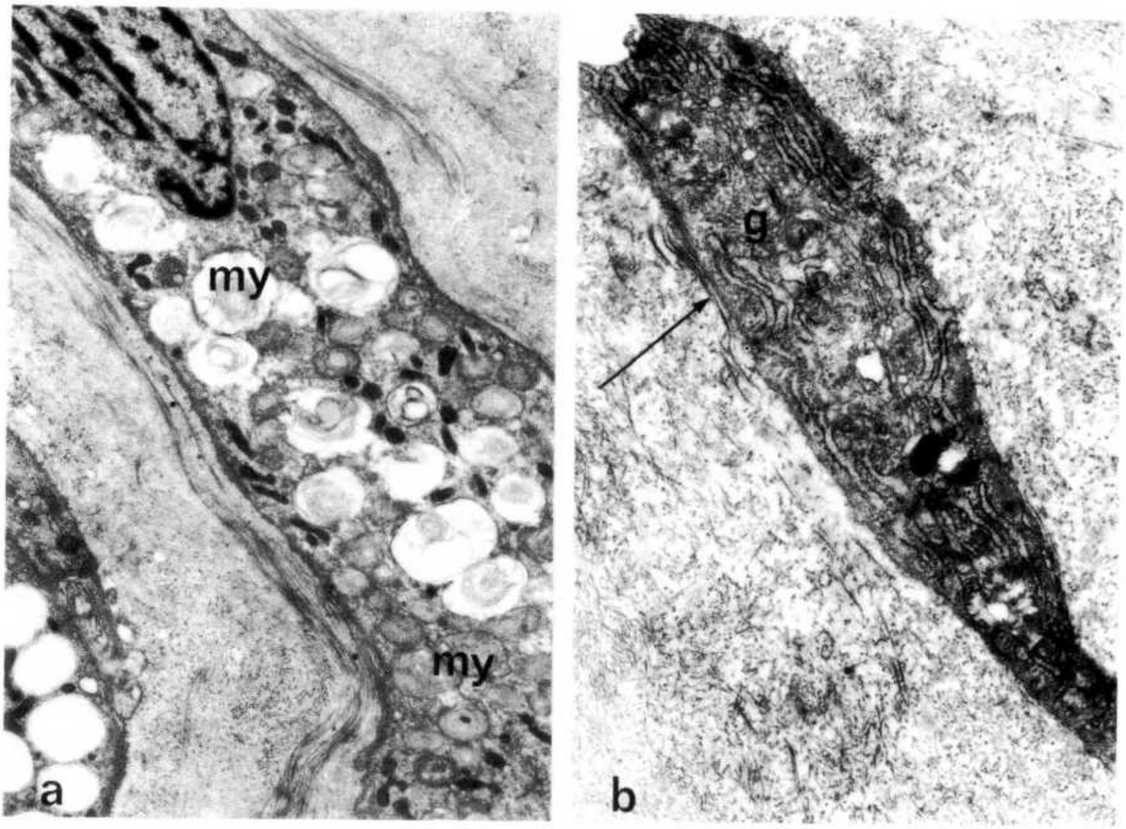

Fig. 18 *Failed graft stroma.* a. *Vacuolation of cytoplasm and development of multiple myelin figures (my) in stromal cells of 10 months old lamellar graft. (×7500).* b. *In the same graft a fibroblastic cell with prominent cytoplasmic organelles is located within a pocket of short disorganised collagen fibrils. Some fibrils (arrow) are aligned along the cell membrane, close to the Golgi complex (g). (×11 900).*

changes. These cells appeared to be universally more active in terms of cell size, distribution of nuclear chromatin, and prominence of cytoplasmic organelles in comparison with stromal cells in normal unoperated corneas. Some showed signs of necrosis with grossly distorted nuclei, disintegration of organelles, and rupture of the plasma membrane. In case 3 many stromal cells appeared rounded and contained myelin figures and cytoplasmic vacuoles with extracted contents (Fig. 18a). In both cases 2 and 3 active cells were often located within distinct pericellular zones of short, randomly orientated collagen fibrils; these fibrils were sometimes closely apposed to the cell membrane and adjacent to the secretory organelles (Fig. 18b).

Discussion

The corneal melting syndrome of Mooren is clinically quite distinct from other forms of peripheral corneal ulceration such as those associated with systemic vasculitis, rheumatoid arthritis, polyarteritis nodosa, and Wegener's granulomatosis. It is essentially a painful, bilateral condition which is not associated with any systemic disease and which involves progressive peripheral, then central, destruction of the corneal stroma. Mooren's and other forms of peripheral corneal disease both begin with limbal inflammation and ulceration. An important difference, however, is that except in extreme cases of peripheral ulceration only Mooren's ulcers progress centrally and, unlike these other forms of ulceration, never invade adjacent scleral tissue. A characteristic feature of this disorder, seen in all cases reported here, is that, while the corneal periphery is opaque, deeply ulcerated, and extensively vascularised, unaffected tissues beyond the ulcerating front appear transparent and only slightly oedematous. When all the stromal tissue has been destroyed, the pain and inflammatory signs disappear. The cornea is replaced by a thin atrophic scar which is sometimes so thin that limited vision may be possible through it. Perforation of the cornea due to Mooren's ulcer, as in the 3 patients described here, is very unusual and is considerably less common than perforation due to other forms of corneal disease. Furthermore, corneal grafts are well tolerated in these latter cases provided the systemic condition is under control, whereas the prognosis for corneal grafts in patients with Mooren's disease is notoriously poor. Although the clinical presentation and course of these 3 patients were typical of the corneal melting syndrome of Mooren, each showed some unique feature.

In all 3 patients the onset was acute, with severe debilitating pain in the affected eye. One patient had some mild premonitory symptoms one year before and another had sustained an injury 5 days previously. All cases were bilateral. The second eye was affected 5 days after the first in case 1, 6 months later in case 2 (at a stage when the first eye was very active), and 5 years later in case 3 following the loss of the first eye. Inflammation of the affected eye was in all cases confined to the limbus, and in no instance was the sclera involved.

On the precept that the limbal conjunctiva adjacent to the ulcer might be contributing to the corneal destruction, excision of limbal conjunctiva was performed in one patient. This effected a transitory improvement only. Conjunctival hooding was also undertaken, and although this produced some temporary relief of pain, the progression of the disease was unaltered.

Corneal grafts are not normally undertaken in the treatment of this condition because of the high frequency of graft failure in these patients and because corneal perforation is relatively uncommon. In all 3 patients described here the corneas perforated, making grafting essential. Unfortunately, none of the grafts, except one performed 18 months ago, has been successful. The nature of graft failure is also of some interest. For the first few postoperative days the grafted cornea remained clear and of normal thickness, after which it rapidly thickened and developed fine epithelial bullae. Grafts may be maintained in this condition either permanently or for many months provided limbal inflammation is prevented by continued use of local steroids. More often, however, a gutter develops at the periphery of the newly transplanted tissue. In one instance this was at the margin of a smaller graft inserted within an earlier, failed graft. In another it appeared at the margin of an 8 mm graft, adjacent to original host tissue. It is of considerable interest that, in the anterior segment graft which was performed, ulceration recommenced at the periphery of the donor cornea, but at no time was the donor sclera or the junction between host and donor sclera affected. The interval between successive rejection episodes was shorter with increased numbers of grafts, but good tissue matching gave no obvious improvement in retention of the graft. Steroid therapy either in large systemic or local doses had some effect in reducing inflammation, but most grafts still opacified or became thin, scarred, and semitransparent.

Although the clinical appearance of typical Mooren's ulcer is well known, in contrast attempts to describe the histopathological features of this disorder have not found universal agreement. In particular, considerable variation has been reported concerning the extent of inflammation associated with the ulcer. This ranges from the presence of few inflammatory cells, but an increased number of stromal keratocytes,[4] to ulcers containing lymphocytes and polymorphonuclear (PMN) leucocytes,[5] and to a case where PMN leucocytes were virtually the only type of infiltrating cell in cornea and conjunctiva.[6] Except in case 1, where bacterial infection was detected in the early course of the ulcer, the low incidence of PMN leucocytes was a conspicuous feature of all excised tissue in our patients. This is remarkable, particularly in relation to the absence of epithelium and Bowman's layer at the ulcer foci, in view of experimental studies where disruption of the corneal surface actually appeared to stimulate invasion of the stroma by PMN leucocytes.[8] The nature and timing of the stimulus for such infiltration are, however, little understood. PMN leucocytes are known to contain abundant lysosomal hydrolase enzymes, including collagenase,[9 10] and have been highly implicated as agents of corneal matrix destruction in one ultrastructural study of Mooren's disease.[6] However, in our ultrastructural studies of the region of active ulceration in 3 cases corneal matrix destruction was located in the presence of fibroblast-like cells, possibly activated cells of the corneal stroma.

The presence of large numbers of lymphocytes and plasma cells as seen in the conjunctival stroma of our 3 cases was also reported in ulcers described previously.[5 11 12] This observation would seem to substantiate the view of conjunctival function as that of a local lymph node.[13] In addition several authors using immunofluorescence techniques have shown positive staining for immunoglobulins in the conjunctival epithelium and stroma during this disease.[6 11 14] No positive staining for IgG was observed in a conjunctival biopsy from case 3, studied by this method. However, the presence of cell mediated immunity to conjunctival and corneal tissue was suggested by a positive result in an in-vitro lymphocyte stimulation assay. Other workers have also demonstrated cell mediated immunity in Mooren's disease using this method.[6 11 15]

The conjunctiva has been implicated as a possible source of proteolytic enzymes presumed responsible for corneal destruction.[5] Brown showed lysis of collagen gels cultured in the presence of conjunctival stroma from patients with Mooren's disease. In addition, a high percentage, though not all, of ulcers treated by conjunctival excision showed improved healing, possibly due to the removal of the sites of enzyme production.[2 16] However, the role of the conjunctiva as a source of proteolytic enzymes involved in corneal ulceration is questionable for several reasons: firstly, this study and others[5 11 12] have failed to demonstrate concentrations of conjunctival granulocytes or, on morphological criteria, other active cells which might represent the secretory machinery for such enzyme production; secondly, were sufficient enzymes released to mediate destruction of adjacent corneal tissue, one might reasonably expect the conjunctival stroma to show similar destructive changes, but this is not the case.

No previous ultrastructural studies of the limbal cornea in Mooren's disease have been reported. In one case where this was possible here, an interesting stratified organisation was evident. The salient feature of this region was an increase in the extent of stromal matrix destruction from the deeper layers outwards. This ranged from essentially intact deep stroma, infiltrated with macrophages, through the increasingly disorganised mid stroma containing active fibroblasts, to the outer layers where extensive degradation of stromal collagen fibrils and necrosis of fibroblasts was present. The damaged outer stroma contained conspicuous perivascular accumulations of lymphocytes and plasma cells.

The 3 corneal ulcers examined all illustrated the typical topography of Mooren's disease, with de-epithelialised active zones and undermined central edges, where the overlying epithelium was much thickened. It should be emphasised that no concentrations of infiltrating cells were located at the ulcer foci. Instead, destruction of the superficial stroma was taking place in the presence of fibroblastic cells, while the deeper lamellae remained undisturbed. This situation prevailed both in the original ulcer and where peripheral ulceration recurred following grafting. It is also significant that failed grafts were similarly characterised by the absence of inflammatory leucocytes and by stromal cells, which appeared highly active in terms of their gross morphology and well developed organelles. These graft fibroblasts were apparently engaged in remodelling their surrounding matrix. We conclude therefore that, in these 3 patients with corneal melting syndrome of Mooren, destruction of both host and graft corneal stroma seemed to be dependent on the activity of fibroblastic cells. However, the modulation of corneal fibroblast activity by inflammatory cells at the limbus must be considered. This is vitally important in view of evidence from recent in-vitro experiments which suggests that diffusible factors, released by a variety of cell types in culture, including lymphocytes and macrophages, are able to enhance the capacity of connective tissue cells to degrade their matrix.[17 18] If similar mechanisms are involved in the pathogenesis of Mooren's disease, they may be directed specifically at cells in the corneal stroma, because adjacent scleral tissue, whether of host or donor origin, remains unscathed.

The authors gratefully acknowledge the support by a grant from the Wellcome Trust.

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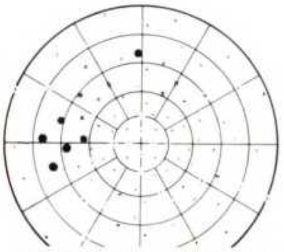

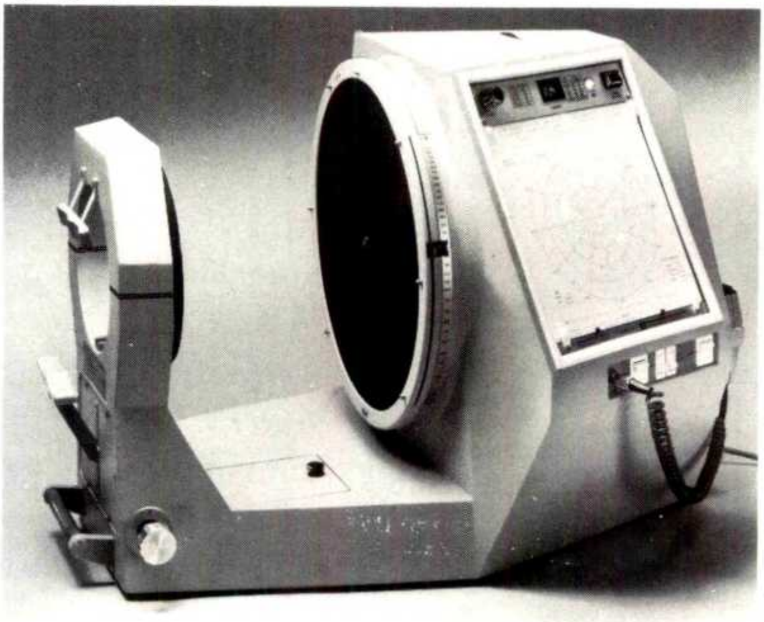

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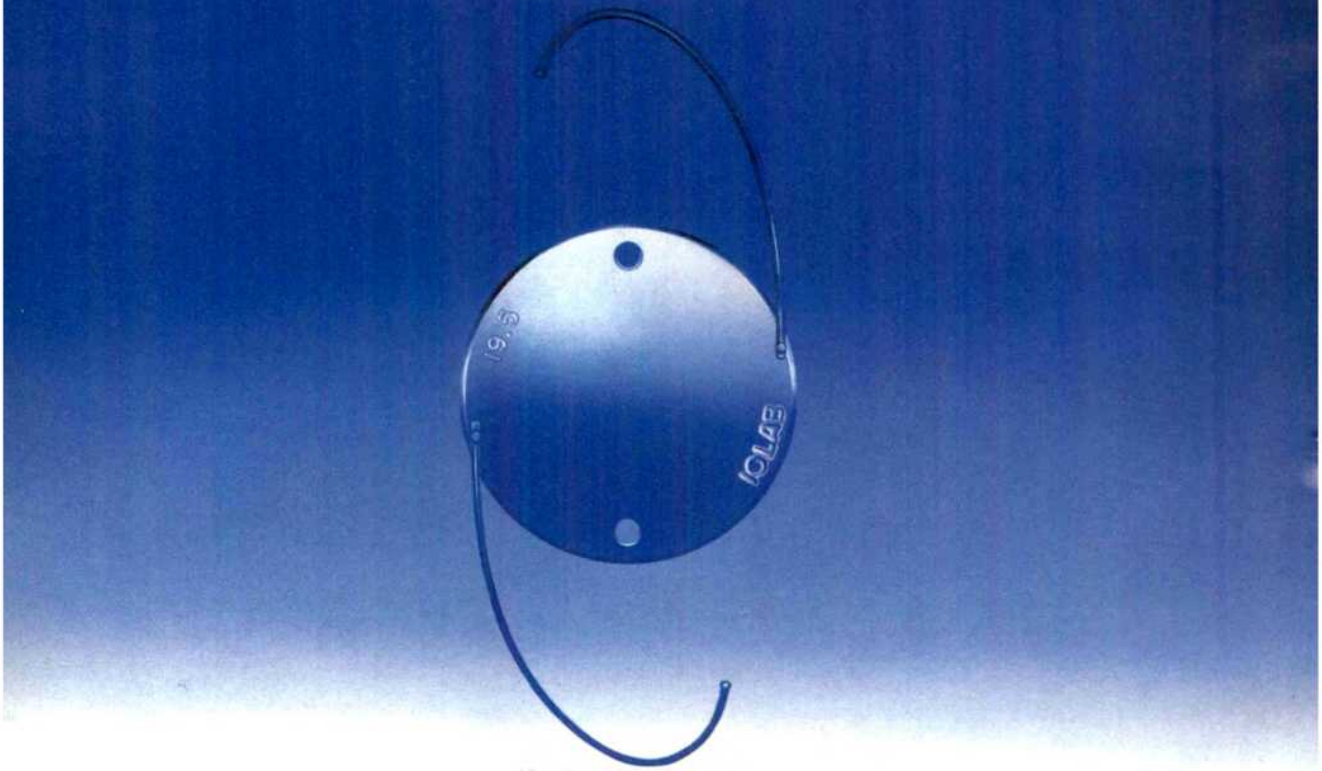

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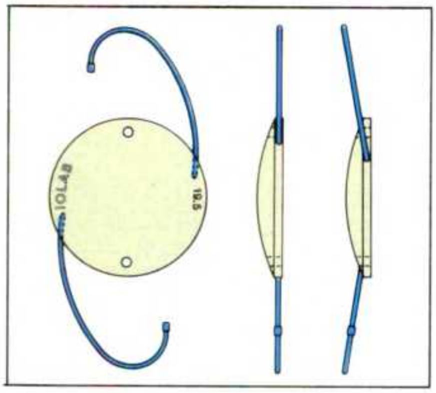

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Aetiology and treatment of acute bacterial infection of the external eye

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SUMMARY The microbial flora of 738 patients with acute bacterial conjunctivitis, corneal ulceration, blepharitis, dacryocystitis, and discharging sockets has been investigated. *Staphylococcus aureus, Streptococcus pneumoniae*, and *Haemophilus influenzae* were the main pathogens isolated. *Str. viridans* was associated with conjunctivitis in patients aged under 1 year. *Moraxella sp.* was isolated on only one occasion. Overall, 40% of specimens were associated with *Staph. epidermidis* or mixed skin flora, which also occurred with cultures of the normal eye. *Clostridium welchii* was isolated on 3 occasions but was not associated with bullae or gas gangrene. The least overall resistance, of 6%, was to chloramphenicol, but no one antibiotic was effective against all pathogens. Gentamicin remains the antibiotic of choice for *Pseudomonas aeruginosa* infection.

The bacterial pathogens causing acute infection of the external eye, and their pattern of antibiotic sensitivity, have not been investigated recently in the United Kingdom, though they have been in the United States of America.[1-3] Initial antibiotic treatment is on an arbitrary basis, often without preceding cultures, and is necessarily based on previous work.[4] However, types of pathogenic bacteria are gradually changing, as are their antibiotic sensitivities, often resulting from plasmid transfer of inactivating enzymes. We carried out the present study to identify current pathogens in various acute conditions and to determine the most appropriate topical antibiotics with which to treat them.

Materials and methods

Patients were examined and clinical data recorded in the Casualty Department and Outpatient Clinic of Southampton Eye Hospital during January to December 1980. Eyes were sampled by culturing conjunctivae or lid margins with sterile cotton-wool swabs, which were placed in Stuart's transport medium for transfer to the laboratory. Second swabs were collected for anaerobic culture and were placed directly into thioglycollate broth.

Aerobic culture was performed on chocolate agar in 5% CO_2 in air at 37°C for 48 hours; fluid enrichment medium was not used, as we wished to establish the *predominant* aerobic bacterial flora on a semi-quantitative basis. Anerobic culture was carried out by incubating the thioglycollate broths for one week at 37°C and then subculturing them on to blood agar, supplemented with cystine and menadione, incubated anaerobically for 48 hours. Bacteria were identified by standard laboratory methods.[5] Antibiotic sensitivity testing was performed by Stokes's control method with discs[6] with tetracycline, neomycin, and gentamycin at 10 μg, chloramphenicol at 50 μg, and sulphacetamide at 100 μg.

Control cultures were taken from normal volunteer students and staff in the hospital.

Results

The percentage isolation rates of aerobic bacteria for each clinical condition are given as pure and mixed growths in Table 1. Isolation rates of anaerobic bacteria are similarly given in Table 2. The percentage rates of antibiotic resistance for the various bacteria isolated as 'pure growths' above are listed in Table 3, together with the overall resistance rate to each antibiotic.

Discussion

Staphylococcus epidermidis was isolated in pure growth from 57% of normal conjunctival controls and

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Table 1 *Aerobic bacterial growth*

Clinical condition	*Pure bacterial growth*								*Mixed bacterial growth*						*No growth*	*Total number of eyes/sockets*
	Staph. aureus	*Staph. epidermidis*	*Str. pneumoniae*	*Str. viridans*	*Enterococci*	*Haemophilus influenzae (Koch-Weeks bacillus)*	*Moraxella sp. (Axenfeld bacillus)*	*Coliform sp.*	*Staph. aureus+ Staph. epidermidis*	*Staph. aureus+ Str. pyogenes*	*Staph. aureus+ Str. pneumoniae*	*Haemophilus influenzae+ beta haemolytic str.*	*Mixed coliforms sp.*	*Mixed skin flora (diphtheroids, Neisseria sp. Str. viridans)*		
Conjunctivae																
Normal controls	23	57	0	0	0	0	0	0	0	0	0	0	0	0	20	30
Conjunctivitis																
under 1 year	30	2	8	12	2	12	0	15	0	2	3	5	2	6	1	118
1 to 80 years	23	39	4	1	0	5	0	5	0	0	0	1	0	6	16	409
Corneal ulceration	17	12	2	0	2	0	0	3	0	0	0	0	0	27	37	66
Dacryocystitis	32	32	10	0	0	3	0	3	0	0	0	0	0	4	16	31
Discharging socket	36	10	0	0	9	0	0	27	0	0	0	0	0	18	0	11
Lids																
Normal controls	7	50	0	0	0	0	0	0	27	0	0	0	0	0	17	30
Blepharitis	26	34	2	0	0	1	1	3	3	0	0	1	0	11	18	103

All figures given are percentages of the total for each group.

Table 2 *Anaerobic bacterial growth*

Clinical condition	*Clostridium perfringens (welchii)*	*Anaerobic cocci*	*Total number of eyes*
Conjunctivitis			
under 1 year	0	0	7
1 to 80 years	1*	2	103
Blepharitis	0	3	30
Dacryocystitis	3*	0	27
Corneal ulceration	3*	3	28
Discharging socket	0	0	3

All figures given are percentages of the total for each group.
*Not associated with gas gangrene.

50% of normal lid controls. *Staph. aureus* was found in 23% of normal conjunctival controls as a pure growth, but in 27% of normal lid controls as a mixed growth with *Staph. epidermidis*; it was, however, found predominantly as a pure growth in blepharitis. Perkins *et al.*[1] found a *Staph. epidermidis* rate of 70% and a *Staph. aureus* rate of 13% in their normal conjunctival controls, which compared with other studies. The normal conjunctiva is thus usually colonised with *Staph. aureus* or *epidermidis* with a propensity for a pure growth of either, which needs to be considered when reviewing results of cultures of eye swabs. However, streptococci, haemophili, and coliforms were never isolated from normal conjunctivae and lids. While we failed to isolate anaerobic bacteria from our normal eyes, Perkins *et al.* did so in a different fluid-enriched medium, finding *Propionibacterium acnes* in 44%, peptostreptococci in 6%, and *Clostridium* sp. in 1%. It is known, however, that there is an anaerobic environment within the lacrimal duct,[7] which is their probable source, rather than the conjunctiva, which has an aerobic environment.

We have previously investigated the bacterial flora in ophthalmia neonatorum[8] and isolated predominantly *Streptococcus viridans* and *Haemophilus influenzae*[9] when compared with controls, as well as *Staph. aureus* and *Chlamydia trachomatis*. We have now isolated similar pathogens, except chlamydiae, in children under 1 year old with acute conjunctivitis, as well as isolating *Str. pneumoniae* and coliform bacilli. However, we have not isolated *Str. viridans* from children over 1 year old or from adults with acute conjunctivitis, suggesting that it then ceases to be pathogenic to the conjunctiva. Mixed growths of staphylococci or haemophili with streptococci occurred in conjunctivitis only in children under 1 year. No cases of conjunctivitis were due to gonococci, meningococci,[10] moraxella,[11] or *Aereomonas hydrophilia.*[12] However, *Clostridium perfringens (welchii)* was isolated from one case and

Table 3 *Antibiotic resistances of bacteria isolated in pure growth*

	*Staph. aureus**	*Streptococci*	*Haemophilus influenzae*	*Coliform sp. inc. Pseudomonas*	*Clostridium perfringens (welchii)*	*% overall resistance*
Chloramphenicol	2	0	0	35†	0	6‡
Tetracycline	5	7	0	31†	0	9‡
Gentamicin	2	100	8	2	100	19
Neomycin	3	100	6	6	100	20
Sulphafurazole	12	8	39	42†	0	22‡
Total numbers	189	54	36	52	3	334

All figures given are percentages of the total for each group.
*76% resistant to penicillin.
†15% innate resistance of *Pseudomonas aeruginosa.*
‡2·4% innate resistance of *Pseudomonas aeruginosa.*

anaerobic cocci from another 2, but there was no evidence of gas gangrene or anaerobic cellulitis.

The 27 cases of dacryocystitis all had a similar flora to conjunctivitis in the adult, though it may be primarily due to an actinomycete.[7]

We cultured 66 eyes with different types of corneal ulceration thought to be bacterial in origin, but 24 yielded no growth. In the remainder we had similar isolations to those from conjunctivitis in the adult, except *Haemophilus influenzae*, which was not isolated in association with corneal ulceration. No cases were due to beta haemolytic streptococci[13] or *Pseudomonas* sp.[14] One case occurred from which *Clostridium perfringens* was isolated, but it was not associated with a bulbous lesion or a frothy coagulum.[15]

Discharging sockets were associated with *Staphylococcus aureus*, coliform spp., mixed skin flora, and enterococci. This is similar to the findings of Christensen and Fahmy.[16]

Both *Staphylococcus aureus* and *epidermidis* were isolated in pure growth from patients with blepharitis, but the significance of the *Staph. epidermidis* is doubtful, as it was present at a higher percentage in controls (50% controls versus 34% patients). This was not the case with *Staph. aureus* (7% versus 26%), whose isolation was thus significant ($\chi^2=5{\cdot}1$, $0{\cdot}05>p>0{\cdot}01$). However, chronic staphylococcal blepharoconjunctivitis can be due to *Staph. epidermidis* in compromised hosts.[17] Occasional isolates of other pathogens occurred, including *Moraxella sp.*, which is usually associated with chronic blepharoconjunctivitis[11] but can be isolated from chronic corneal ulcers.[18] There were no further cases of *Streptococcus pyogenes* gangrene (necrotising fasciitis) of the lids.[19]

Chloramphenicol has remained the most effective antibiotic for topical treatment of infection of the external eye with the least overall resistance of 6%, while tetracycline was the next most effective, with a comparative overall resistance of 9%. Both chloramphenicol and tetracycline were less effective with coliform bacilli, for which the antibiotic of choice is gentamicin. It has previously been suggested that chloramphenicol drops should be instilled hourly when treating conjunctivitis and that preparations also containing corticosteroid should *not* be used for treating superficial infections of the eye.[4] Gentamicin remains the treatment of choice for *Pseudomonas aeruginosa* infection, but streptococci are resistant to it and contributed to the higher overall resistance. However, most ocular infections were caused by *Haemophilus influenzae, Staphylococcus aureus,* or *Streptococcus pneumoniae* or *viridans*, all of which are sensitive to chloramphenicol, which remains the most effective topical antibiotic for 'routine' use.

We thank the clinical staff at the Eye Hospital for examining the patients and collecting the swabs, and the technical staff of the laboratory for processing them. We thank our colleagues M. J. Absolon, I. H. Chisholm, A. R. Elkington, and C. B. Walker for allowing their patients to be included in this study. We thank Miss P. J. Stoffell for typing the manuscript, and also Mrs S. B. McGill.

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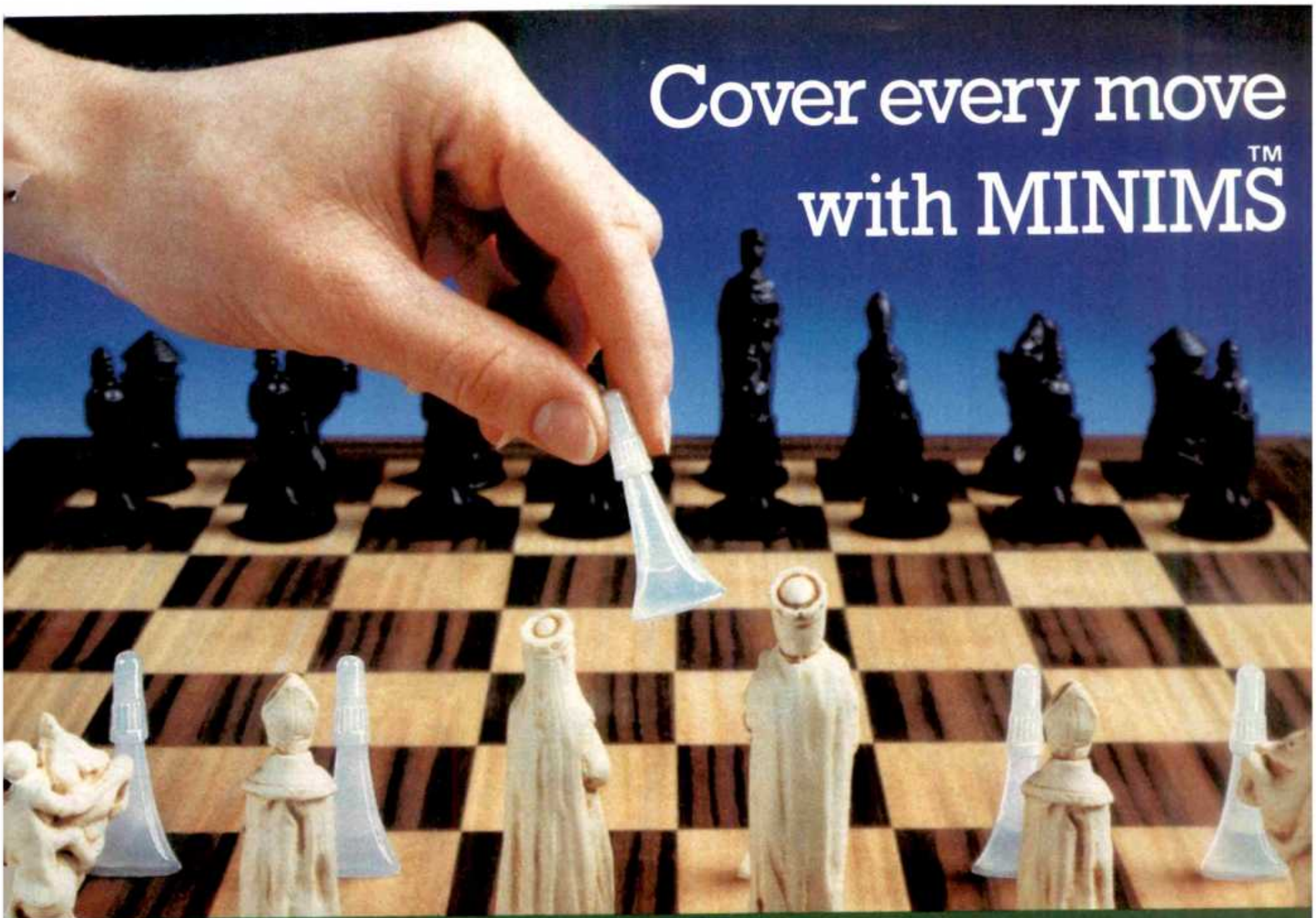

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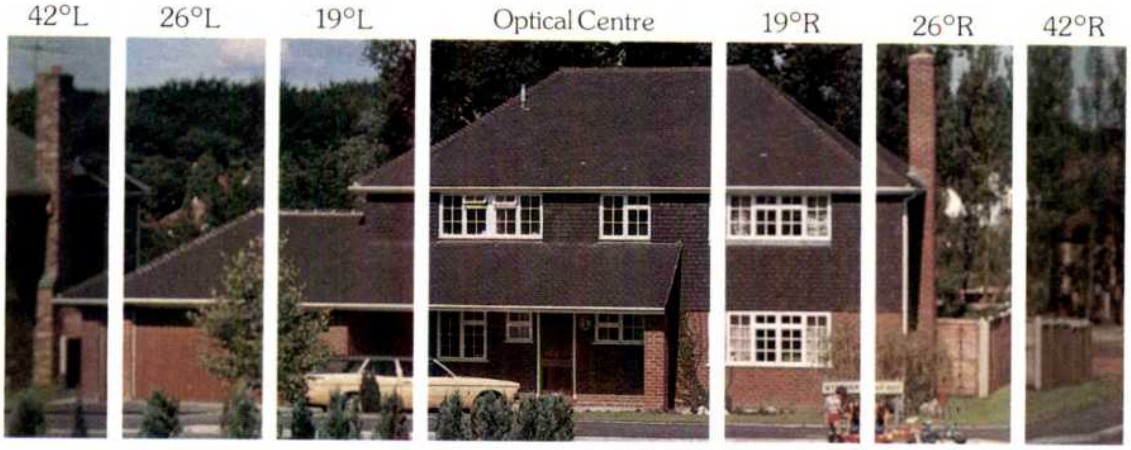

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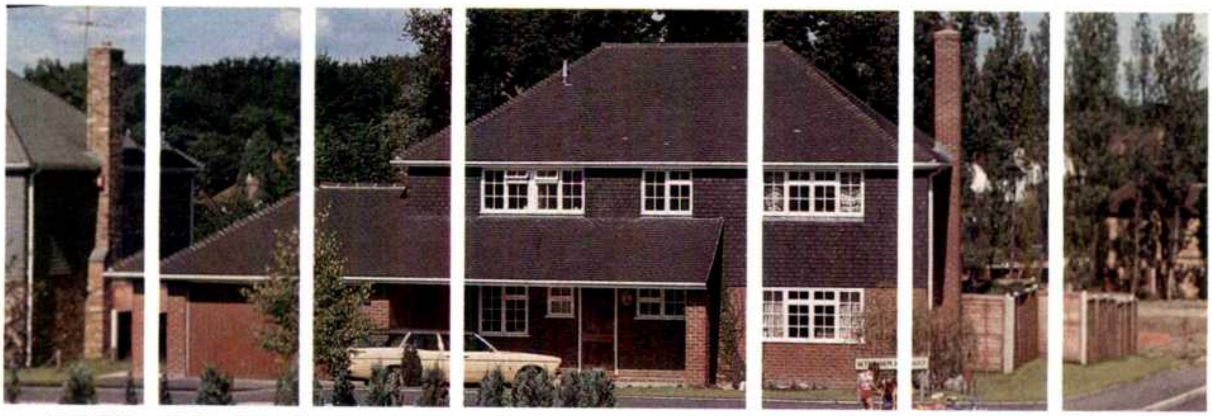

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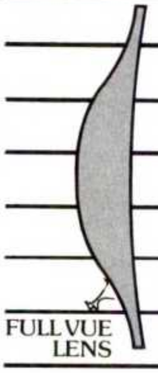

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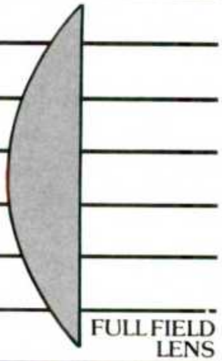

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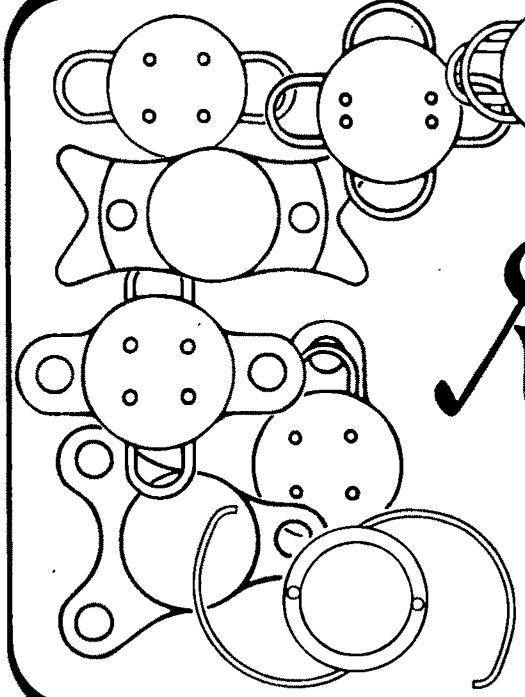

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British Journal of Ophthalmology, 1982, **66**, 361–363

A randomised double-blind clinical trial of acyclovir (Zovirax) and adenine arabinoside in herpes simplex corneal ulceration

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From [1]St Paul's Eye Hospital, Liverpool, and the [2]Wellcome Research Laboratories, Beckenham, Kent

SUMMARY A double-blind clinical trial of 3% acyclovir (Zovirax) and 3% adenosine arabinoside (ara-A, Vidarabine) in 93 patients with herpetic corneal ulceration is presented. Ulcers in 45 (94%) of acyclovir-treated patients and 37 (82%) ara-A-treated patients healed within 14 days. Patients treated with acyclovir healed more rapidly than those treated with ara-A ($p<0.01$). No serious adverse effects were observed.

Acyclovir (Zovirax) is a potent and selective antiherpes virus agent when it is phosphorylated into its active form by a virus specified thymidine kinase.[1 2]

Initial evidence of action against human herpes simplex infections was obtained by Jones *et al.*[3] in 1979. Subsequently double-blind studies of its use in herpetic corneal ulceration have shown acyclovir to be at least as effective as idoxuridine (IDU)[4 5] or trifluorothymidine (F3T).[6]

Adenosine arabinoside (ara-A) was first synthesised in 1960 as an anticancer agent and originally investigated with this application in mind.[7] In herpetic corneal ulceration ara-A is as effective as IDU[8] and F3T.[9] This report describes a double-blind clinical trial comparing acyclovir with adenosine arabinoside in herpetic keratitis.

Patients and methods

The patients included in this study, seen at St Paul's Eye Hospital, Liverpool, were diagnosed clinically as having herpetic corneal disease by slit-lamp biomicroscopy subsequent to staining with rose Bengal. At the initial visit corneal swabs were taken from all patients for culture of herpes simplex virus in Vero cells at 35°C. Patients excluded from the trial were those who were less than 16 years of age, were pregnant, had a corrected visual acuity of 6/24 or worse in the contralateral eye, were unable to attend regularly for follow-up, or had received other antiviral medication for their current attack. Full ocular examinations were carried out at presentation and during follow-up assessments by one of 2 ophthalmologists. When possible a given patient was assessed by the same observer. Assessment of efficacy was planned for days 2, 4, 6, 8, 11, and 14 of treatment. Patients were required to fill in cards to record their use of the ophthalmic ointment.

Treatment with either 3% acyclovir or 3% ara-A 5 times daily was assigned randomly to patients. The ophthalmic ointments were provided in identical tubes bearing a trial number, and the entire study was carried out in a double-blind manner. Therapy was continued at least until the epithelial defect had healed. If the ulcer increased significantly in size over 3 days, remained static for 7 days, or had failed to heal within 14 days, the patient was crossed over, under the direction of the chief pharmacist, to the alternative medication. Patients already receiving local steroids at presentation and those presenting with amoeboid ulceration were included in the study, but separate consideration was given to them in the analysis of results.

If any patient's ulcer reappeared at the same site within 14 days of stopping therapy, it was designated a recrudescent ulcer and was treated with the alternative trial drug. Ulcers appearing after 14 days were designated recurrent ulcers and were treated with the same coded antiviral treatment. Patients were reviewed 6 months after therapy was terminated.

Results

Forty-five patients received ara-A and 48 patients received acyclovir ophthalmic ointment. The

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Table 1 *Distribution of patients according to ulcer type*

Ulcer	*Acyclovir*	*Ara-A*
Simple dendritic	40	39
Steroid treated dendritic	2	4
Amoeboid	6	2

Table 2 *Patients' characteristics at presentation*

Patients' characteristics	*Acyclovir*	*Ara-A*
Sex: male	32	30
female	16	15
Average age	51	52
Duration of symptoms:		
1 week or less	39	37
2-3 weeks	5	6
4 weeks or greater	4	2
Ulcer size:		
large	dendritic 16 (38%) amoeboid 3	dendritic 19 (44%) amoeboid 1
multiple small	dendritic 13 (31%)	dendritic 10 (23%)
small	dendritic 13 (31%) amoeboid 3	dendritic 14 (33%) amoeboid 1
History of cutaneous herpes (% of patients)	42%	42%
Primary ocular infection	35%	59%
Recurrent ocular infection	65%	41%

numbers of patients presenting with each type of ulcer are given in Table 1.

Before the significance of the results was assessed it was important to establish that the groups of patients were similar, especially with respect to factors likely to affect healing rate. The groups were well matched in terms of sex, age, duration of symptoms before presentation, and ulcer size at presentation. There was no significant difference in the numbers presenting with initial or recurrent attacks ($p<0{\cdot}05$, Fisher's exact test, $\chi^2=3{\cdot}101$). The data are presented in Table 2. Patient compliance as indicated by their diary cards was 94% in the acyclovir group and 95% in the ara-A group. Laboratory confirmation of the diagnosis by culture from corneal swabs was positive in 38% of cases.

In the acyclovir-treated group 3 ulcers failed to heal. One patient aged 74 years who had symptoms for 4 weeks presented with 2 large dendritic ulcers from which herpes simplex virus was isolated. The ulcers remained active after 14 days and resolved after a 10-day course of ara-A. The second patient, receiving steroids at entry, had a large dendritic ulcer which responded poorly to both antiviral agents; he was admitted and removed from the trial on day 26 because of increasing stromal infiltration.

The third patient aged 74 presented with a large amoeboid ulcer on a 6-month-old corneal graft. The ulcer was designated cured on day 14 but recurred 3 weeks later and responded unsatisfactorily to acyclovir. In the ara-A group 8 patients failed to respond satisfactorily to therapy. Seven of the ulcers were simple dendritic and one was an amoeboid ulcer. Five of the dendritic ulcers and the amoeboid ulcer were treated with acyclovir and all healed in an average of 7 days (range 4-12 days).

The time to complete healing for all patients ranged from 2 to 14 days. A logrank analysis was performed on the healing time data for acyclovir and ara-A, and a significant difference was found in favour of acyclovir ($p<0{\cdot}01$). This level of significance was achieved when the dendritic ulcers were considered alone and when all ulcers were considered as a group. A graph representing the cumulative healing rate for dendritic ulcers is presented in Fig. 1.

Two patients with amoeboid ulcers were entered into the ara-A group. A large ulcer failed to heal, while a small ulcer healed in 6 days. Six amoeboid ulcers were treated with acyclovir and five healed in

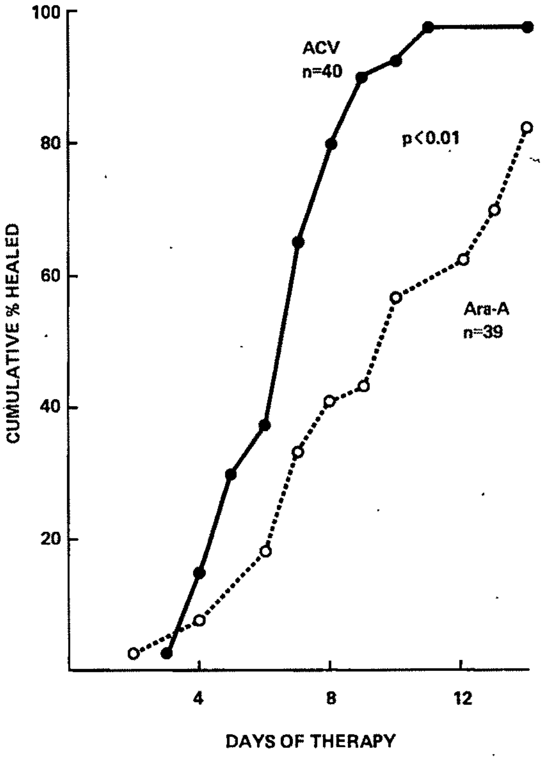

Fig. 1 *Cumulative frequency distribution of percentage healing rate for patients with dendritic ulcers treated with acyclovir (ACV) and adenine arabinoside (ara-A).*

Table 3 *Response to therapy according to ulcer size and type*

Ulcer	*Size*	*Acyclovir mean healing time (days)*	*Failed*	*Ara-A mean healing time (days)*	*Failed*
Dendritic:	small	6·2	–	8·5	–
	multiple	6·2	–	8·5	2
	large	7·5	2	10·5	6
Amoeboid:	small	6·0	–	6·0	–
	large	8·0	1	–	1

an average of 6·6 days. Of 3 large ulcers, one failed to heal and 2 healed in an average of 8 days. Of the 3 small ulcers all healed in an average of 6 days. This group was too small and unbalanced to carry out further analysis. Table 3 shows the average healing times for each category of ulcer treated in the study and indicates the distribution of treatment failures among these groups.

Two patients developed adverse symptoms during therapy possibly due to their antiviral therapy. One patient on acyclovir experienced an allergic response; this could also have been caused by the atropine drops being administered concurrently. One patient on ara-A complained of grittiness after application of the ointment. No other adverse effect was seen in this group of patients.

Discussion

Acyclovir and ara-A were found to be effective agents for the treatment of dendritic ulceration, and ulcers treated with acyclovir healed more rapidly. As expected, the larger ulcers took longer to heal in both groups and constituted most of the treatment failures. The amoeboid ulcer groups were too small to analyse separately but were less of a problem than during the previous series carried out at this hospital,[9] possibly due to more awareness among general practitioners of steroid-induced complications. Most ulcers responded within 2 weeks and the remainder were given alternative therapy after this time. The incidence of adverse side effects during this relatively short exposure to acyclovir and ara-A was low. One patient on acyclovir experienced an allergic response which might have been due to other concurrent medication. One patient on ara-A complained of grittiness of the eye after application of the ointment.

A number of antiviral agents have been found to be effective in treating dendritic ulceration, but acyclovir is apparently superior in providing more rapid healing. A similar study[10] comparing acyclovir with ara-A showed a faster healing rate for acyclovir, which did not reach statistical significance. This may have been due to the smaller number of patients included and the larger proportion of small ulcers in the ara-A group, which tend to heal more rapidly.

The need for a potent nontoxic antiviral agent which can be used for long periods in deep corneal disease is obvious. The fact that 3% acyclovir ointment penetrates into the anterior chamber in therapeutic levels[11] and has been used systemically to clear a hypopyon in advanced herpetic corneal disease[12] indicates its promise in patients who manifest recalcitrant ulceration and keratouveitis.

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British Journal of Ophthalmology, 1982, **66**, 364–367

Antimicrobial activity of topical anaesthetic preparations

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SUMMARY Eight commercial topical anaesthetic preparations were tested for their ability to inhibit microbial growth in vitro by incubating serial dilutions with each of 4 micro-organisms. In addition corneas of mice were infected with *Staphylococcus aureus*, and the effect of the anaesthetics on isolation rates of bacteria was investigated. The preparations were shown to have a wide range of antimicrobial activity, correlating both with the active agents and the preservatives. We suggest that some preparations are unsuitable for use prior to collection of specimens from human corneal ulcers.

The successful management of corneal infection depends on the early commencement of specific antimicrobial chemotherapy. Since this requires the prompt identification of causative micro-organisms, the procedure for specimen collection must ensure no loss of viability of these agents.

Material for culture from infected corneas is often collected after application of a topical anaesthetic. Usually only a small amount of material is obtained, giving a light growth of bacteria or fungi. An anaesthetic preparation with considerable antimicrobial activity might lead to a dangerous false negative culture result.

A range of topical preparations is available to ophthalmologists; multidose containers of anaesthetic and preservative and single-dose vials containing the anaesthetic agent only. The antimicrobial activities of the anaesthetic agents and preservatives have been determined separately in vitro,[1–3] and several clinical trials of anaesthetics during bronchial and odontological procedures have been reported.[4–6] We determined the antimicrobial activities of 8 commercially available topical anaesthetics in vitro, using a minimum inhibitory concentration (MIC) assay and used a mouse model of corneal infection to test the effect of the preparations on the recovery of viable bacteria.

Materials and methods

MINIMUM INHIBITORY CONCENTRATION ASSAY

Four clinical isolates each of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, and *Candida albicans* were selected, as these organisms are commonly found in infected corneas. Single colonies were cultured overnight in Mueller-Hinton broth (*Staph. aureus* and *Ps. aeruginosa*), Todd-Hewitt broth (*Str. pneumoniae*), or Sabouraud broth (*C. albicans*).

Eight commercial preparations were assayed. These are set out in Table 1.

The microbial suspensions were subcultured and reincubated for 3 hours. Serial 2-fold dilutions of the anaesthetic preparations were made in the appropriate broth in microtitre trays. An equal volume of suspension (50 μl) containing 10^5 organisms in the log phase of growth was added to each well, and the trays were incubated for 18 hours at 37°C. Growth of organisms was defined as the appearance in a well of an aggregate larger than 2 mm in diameter. Loopfuls from the no-growth wells were plated out on to blood agar to give the maximum microbicidal dilution.

IN-VIVO ASSAY

The animals chosen were F1 (Balb/c×C57B1) mice. A *Staph. aureus* strain (penicillin-resistant, phage type 55/71) isolated from a human corneal ulcer was used to infect the mice.

The animals were given ketamine intraperitoneally (4 mg). Both corneas of each mouse were incised with a scalpel blade and keratome, and several drops of a concentrated (10^{10}/ml) bacterial suspension were dropped onto the cornea. 24 hours later 80% of the eyes had developed keratitis, and these were used in the test. The eye was prolapsed and a sterile

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Table 1 *Topical anaesthetics*

Commercial preparation	*Active reagent*	*Preservative(s)*
Alcaine (Alcon)	Proxymetacaine 0·5%	Benzalkonium chl 0·01%
Decicain (Winthrop)	Amethocaine 0·5%	Chlorobutanol 0·42%
Novesine (Sandoz)	Oxybuprocaine 0·4%	Chlorhexidine diacetate 0·001% and boric acid 0·2%
Ophthaine (Squibb)	Proxymetacaine 0·5%	Benzalkonium chl 0·01% and chlorobutanol 0·2%
Ophthetic (Allergan)	Proxymetacaine 0·5%	Benzalkonium chl 0·01%
Xylocaine Ophthalmic (Astra)	Lignocaine 4%	Benzalkonium chl 0·004%
Minims amethocaine (Smith & Nephew)	Amethocaine 0·5%	None
Minims benoxinate (Smith & Nephew)	Oxybuprocaine 0·4%	None

Benoxinate≡oxybuprocaine. Amethocaine≡tetracaine. Proxymetacaine≡proparacaine.

platinum spatula stroked 5 times across the cornea. Collected material was transferred directly to blood agar. The spatula was stroked 3 times across the plate, which was immediately streaked out. The test anaesthetic preparation (50 μl) was dropped on to the cornea, and 5 minutes later the eye was gently wiped and the scraping procedure repeated. The plates were incubated overnight at 37°C. Eight eyes were tested in each group.

Results

The maximum inhibitory dilution (MID) and maximum microbicidal dilution (MMD) for each drug for each organism are set out in Table 2. These expressions are more suitable than concentrations when we are dealing with mixtures. Each value was derived from testing 4 different isolates in duplicate. Variation between isolates of one organism rarely exceeded one well. Novesine was generally the most lethal preparation, followed by Alcaine, Ophthaine, and Ophthetic with intermediate antimicrobial activity. The Minims, Decicain, and Xylocaine had low inhibitory power. Novesine was the only preparation with substantial anti-pseudomonas activity. The 2 Gram-positive bacteria had a similar susceptibility pattern, with *Str. pneumoniae* generally more sensitive than *Staph. aureus*. Alcaine and Ophthetic, with identical anaesthetic agents and preservatives, differed in their activity to *Str. pneumoniae* by a factor of about 3. We cannot account for this observation. From this in-vitro work we selected *Staph. aureus* as a suitable organism for the in-vivo test.

The mouse assay results (Table 3) are expressed as the mean ($\bar{x}$) of the difference in colony counts between the scrapings prior to and after application of topical anaesthetic, i.e.,

$$x=\log_{10}(\text{counts } \#1+1)-\log_{10}(\text{counts } \#2+1)$$

Novesine reduced the counts by over 1 log, saline had

Table 2 *Antimicrobial activity in vitro*

Preparation		*Micro-organism* *Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Streptococcus pneumoniae*	*Candida albicans*
Alcaine	MID	640	2	600	20
	MMD	200	2	600	18
Decicain	MID	14	<2	24	2
	MMD	13	–	20	2
Novesine	MID	1340	52	580	64
	MMD	850	15	450	60
Ophthaine	MID	240	2	280	18
	MMD	140	2	180	18
Ophthetic	MID	640	2	190	18
	MMD	90	2	180	18
Xylocaine Ophthalmic	MID	10	2	140	3
	MMD	4	2	45	3
Minims amethocaine	MID	8	2	34	3
	MMD	5	2	26	3
Minims benoxinate	MID	4	<2	18	3
	MMD	3	–	14	3

MID=maximum inhibitory dilution. MMD=maximum microbicidal dilution.

Table 3 *Change in number of viable Staph. aureus isolated from corneas of mice with anaesthetics*

Treatment	$\bar{x}$ (±0·196)
Saline	0·016
Alcaine	0·554
Decicain	0·321
Novesine	1·217
Ophthaine	0·560
Ophthetic	0·974
Xylocaine Ophthalmic	−0·170
Minims amethocaine	0·344
Minims benoxinate	0·168

Least significant difference for $p=0·05$ is 0·565.

little effect on the counts, and Xylocaine actually improved the recovery. To assess the significance of these differences a one-way analysis of variance was performed.[7] This gave an F ratio of 5.084, high enough to conclude that a real difference exists between 2 or more groups as compared with the variation within them. The method of least significant differences[8] resulted in 2 drugs significantly reducing the counts compared with saline; Novesine ($p<0·001$) and Ophthetic ($p<0·01$). For Ophthaine and Alcaine, $p\simeq0·07$. The more stringent method of Dunnett's[9] results in only Novesine significantly reducing counts ($p<0·05$). The difference in the $\bar{x}$ values for Alcaine and Ophthetic is surprising but repeatable.

Discussion

The results indicate that some topical anaesthetic preparations can affect the recovery of organisms from infected corneas. This antimicrobial effect correlates with the presence of preservative. The results for Minims benoxinate (no preservative) and Novesine (benoxinate plus preservatives) show this. The chlorobutanol in Decicain is seen to be relatively ineffective at inhibiting growth or recovery of staphylococcus as compared to benzalkonium chloride at 0·01% or chlorhexidine.

In 1966 Kleinfeld and Ellis[1] found that 0·5% amethocaine, 0·4% benoxinate, 2·5% cocaine, and 0·4% chlorobutanol inhibited growth of *Staph. epidermidis, Ps. aeruginosa*, and *C. albicans* in liquid media. Four years later Schmidt and Rosenkranz[2] reported that lignocaine and procaine would inhibit a wide range of micro-organisms. In 1975 Weinstein *et al.*[3] tested 8 anaesthetics in an MIC assay and found amethocaine and hexylcaine to have the greatest inhibitory power. Our in-vitro results for the 2 Minims preparations may be compared with the results of these authors. The minimum inhibitory concentrations for Minims amethocaine and benoxinate are in agreement with those obtained by Kleinfeld and Ellis[1] using pure preparations, but our findings are at variance with those of Weinstein *et al.*[3] in several respects. Firstly, we find 0·15% benoxinate inhibits growth of *Staph. aureus* and *C. albicans* and 0·025% inhibits growth of *Str. pneumoniae*, whereas Weinstein *et al.*[3] report >1% benoxinate is required to inhibit these 3 organisms. Also our streptococci are more sensitive to amethocaine (0·015% versus 0·5% for inhibition) and our candidas less sensitive to amethocaine (0·167% versus 0·015%). These inconsistencies may reflect different strains, media, and anaesthetic preparations, since the Minims contain stabiliser.

A number of factors could influence the effect of the anaesthetics on organisms in human corneas, including total dosage, dilution by tears, the number of organisms present, and the efficiency of absorption into the diseased area of both the anaesthetic agents and preservatives. From the mouse studies we find that the time the drug is on the eye before culturing is important: counts decrease over the first 10 minutes.

Novesine significantly reduces the isolation rate of *Staph. aureus* from corneal ulcers in mice, and this preparation has a high anti-microbial activity in vitro. It would seem that Novesine should not be placed on a patient's eye prior to collecting material for microbiological study. Ophthetic, Ophthaine, and Alcaine, and any other topical anaesthetic containing benzalkonium chloride at 0·01%, also appear to have an unacceptably high level of antimicrobial activity in this instance.

From these results and previous reports it would appear that Minims benoxinate is the preferred drug for obtaining material for culture. It is also unlikely that Minims amethocaine, Decicain, containing chlorobutanol, or Xylocaine Ophthalmic, containing benzalkonium chloride at low concentration, have any effect on isolation rates of organisms from corneas if not left on the eye for more than 2 or 3 minutes.

It should be remembered that infected corneas are relatively insensitive, and collections can often be made without the use of a local anaesthetic. When this is not possible, any reduction in the number of viable organisms recovered from a cornea due to the anaesthetic agent is probably counterbalanced by the increased amount of material obtainable from an anaesthetised eye. The anaesthetic preparation we choose to use should not compromise our chance of recovering the causative agent.

This work was supported by the Lions Save Sight Research Foundation. The authors are indebted to the staff of the Clinical Microbiology Department at Flinders Medical Centre for their support.

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British Journal of Ophthalmology, 1982, **66**, 368–378

The photomyoclonic reflex: an artefact in the clinical electroretinogram*

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SUMMARY An artefact may appear in the clinical electroretinogram (ERG) that can interfere with the recording and interpretation of the ERG b wave. This artefact, the photomyoclonic reflex (PMR), was studied by covering the eye containing the recording electrode and stimulating the fellow eye. Records obtained by this technique before and after administration of a modified Van Lint lid block demonstrated that most of the PMR is due to a reflex contraction of the orbicularis muscle. The remaining part of the PMR was ascertained by eye movement recordings to be a 1·5° to 3·5° downward and medial eye movement. In most persons the PMR occurs with a latency that is fast enough (59 ms±7 ms) to interfere with interpretation of the b wave under most conditions. The PMR can be minimised in some cases by habituation or conditioned suppression. However, these methods generally do not extinguish the PMR but reduce it enough so that it would not readily be rejected as artefact. In such cases the PMR may produce a wave form that mimics a normal-amplitude ERG but with delayed implicit time.

The electroretinogram (ERG) is a light-evoked gross electrical potential generated by retinal cells and recorded at the cornea. Clinically the ERG is often employed to gain objective information about the status of the neurosensory retina.

Although much has been learned in recent years about the cellular origins of various ERG components, there still is considerable variability in the ERG wave form that reflects significant contributions to the recorded potential from extraretinal sources. For example, Gur and Zeevi,[1] in the course of performing frequency analyses on the human ERG, found that the signal is time-locked to the stimulus only during the first 55 to 60 ms of the response. At that time an additional component, which was not completely time-locked to the stimulus, interfered with the ERG potental. Gur and Zeevi attributed this component to a light-induced eye movement, a photomyoclonic reflex (PMR). They cited unpublished experiments by Bickford *et al.*[2] that were said to demonstrate a reflex clonus of the eye musculature in response to a bright flash of light.

The interference from a muscular light-reflex artefact in the recording of the ERG was first noted by Karpe.[3] In his classic monograph on clinical electroretinography Karpe demonstrated that light-induced reflex 'blinking' can significantly impair ERG recordability and interpretation. For example, using a contact lens electrode and a spring-loaded speculum he attempted to record an ERG from a retinitis pigmentosa patient and obtained a small 'blink artefact,' in the absence of any retinal potentials, which resembled a normal ERG except for its delayed timing.

The existence of reflexive, light-induced blinks is well known to clinical electroretinographers. When the blink artefacts are large, they are readily recognised in ERG records. However, less apparent eye movements that accompany all blinks[4] may also interfere with ERG recordings.[5] These eye movements, which can occur when the lid reflex is small or has been aborted,[4] vary in amplitude and thus could be subtle enough to go clinically unnoticed.

Using the time-locking criterion of Gur and Zeevi[1] we have been able to identify retrospectively a PMR artefact in nearly all the records from our clinical

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*Presented at the 1980 Annual Meeting of the Optical Society of America in Chicago, Illinois, and at the 1981 Annual Meeting of the Association for Research in Vision and Ophthalmology in Sarasota, Florida.

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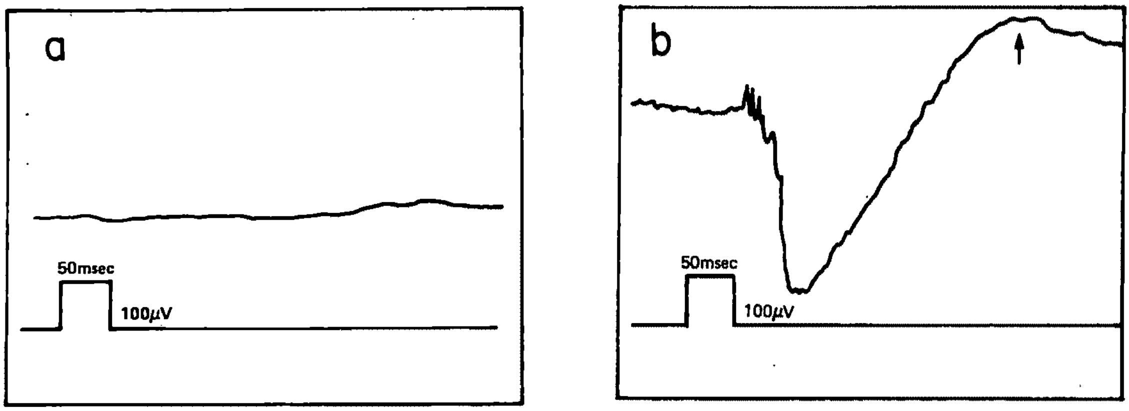

Fig. 1 *A photomyoclonic reflex (PMR) was recorded, uncontaminated by retinal potentials, by occluding the eye containing the electrode and stimulating the fellow eye.* (a) *Control condition; no response was recorded when both eyes were covered.* (b) *A PMR, recorded from the covered experimental eye. The PMR waveform typically consists of spiking followed by a fast corneal-negative, then slow positive, phase (arrow). This reflex has a latency of 55 ms. In all Figures the 10 μs stimulus occurs at the rising edge of the calibration pulse.*

ERG laboratory. Furthermore we have been able to recognise this artefact in several published ERG records from other laboratories. Therefore the present study was conducted to characterise the PMR further and to determine its artefactual contributions to the clinical ERG. Some of the studies reported here are replications of experiments that were designed to investigate other problems or in some cases were technically unsatisfactory. Our results indicate that the PMR artefact can be subtle and can significantly interfere with the interpretation of the clinical ERG.

Materials and methods

ERGs and PMRs to a full-field (Ganzfeld) stimulus were elicited by a 10 μs white flash from a Grass PS-22 variable-intensity stimulator. The luminance for a maximal intensity (I=16) stimulus was $-0{\cdot}26$ log cd. s. m^{-2}. A Burian-Allen bipolar electrode wetted with methylcellulose was used to record the evoked response. The signals were amplified alternating-current coupled (0·1 Hz to 300 Hz) amplifiers. The responses were displayed on a storage oscilloscope, and photographed with a Tektronix C5 oscilloscope camera.

Mydriasis was obtained with 1% tropicamide and 10% phenylephrine hydrochloride. A 0·5% solution of proparacaine hydrochloride was used in all cases as the corneal anaesthetic.

Two neutral-density filters of 1 and 2 log units (nominal) attenuation were used in conjunction with different intensity settings on the photostimulator to determine the intensity-response characteristics of the PMR.

Latencies of PMRs were measured retrospectively from the records of 97 patients who had normal amplitude ERGs. Subjects for the different experimental manipulations included the 2 authors, 2 other normal volunteers, and 3 volunteers who have retinitis pigmentosa (RP). These volunteers gave their informed consent to the experiments.

Results

Properties of the PMR

Six experiments that characterise properties of the PMR are described in this section. For most experi-

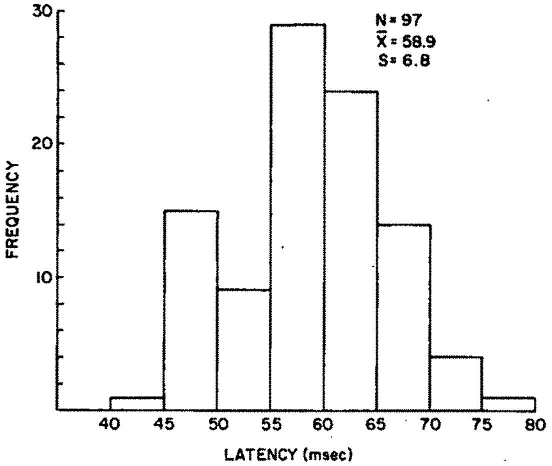

Fig. 2 *Frequency distribution of PMR latencies (mean=59 ms, SD=7 ms) measured from ERG records of 97 patients with normal ERGs.*

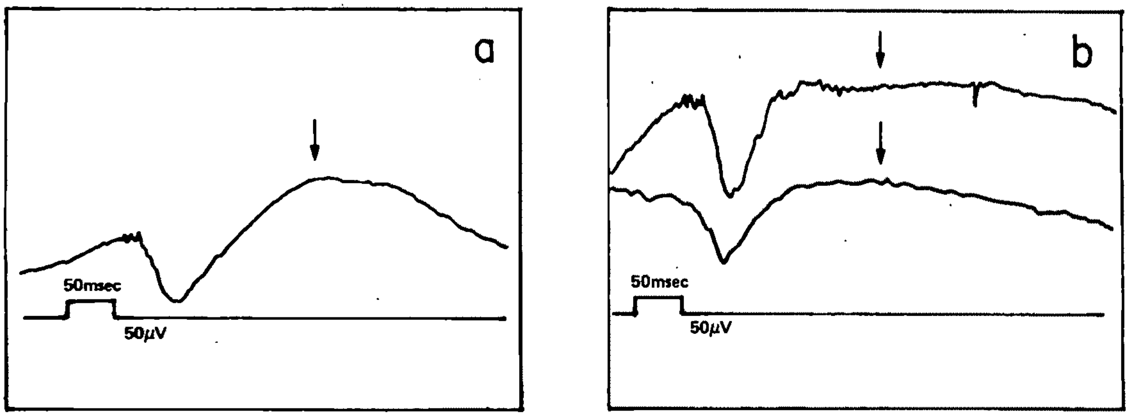

Fig. 3 *The pupillary reflex is the source of the late positive wave of the PMR.* (a) *Arrow points to the late positive phase of a standard-recorded PMR with normal, reactive pupils.* (b) *After mydriatics were instilled 2 PMRs recorded from the subject lacked the late positive waves. Arrows point to areas of the PMR occurring at same point in time as that in* (a).

ments, in order to record the PMR uncontaminated by retinal potentials, the eye with the electrode was occluded and the fellow eye was stimulated.

1. QUALITATIVE FEATURES OF THE PMR

This experiment describes the PMR waveform unobstructed by the ERG.

Procedure. After 20 minutes' dark adaptation a Burian-Allen bipolar ERG electrode was inserted. The eye was then occluded by a cone covered with black photographic tape to prevent exposure to light during the study. To verify the opacity of the cone recordings were obtained with both eyes occluded. The subject sat in a shielded room with his head positioned on a chin rest facing an integrating sphere. A red light-emitting diode (LED) served as a fixation point for the unoccluded eye.

Results. Fig. 1a illustrates the results of the control experiment. No response was recorded when both eyes were occluded. Fig. 1b illustrates the response recorded in the occluded eye during stimulation of the fellow eye. The large corneal-negative deflection has a latency of 55 ms in this subject. The negative deflection is usually, but not always, preceded by spiking activity, and is followed by a slower, positive wave (arrow) that has an average latency of about 160 ms.

The latencies of PMRs measured retrospectively from ERG records of 97 normal patients are presented in Fig. 2. The distribution is bell shaped; the mean is 58·9 ms and the standard deviation is 6·8 ms. The range of PMR latencies is 44·4 to 77·8 ms.

2. PUPILLARY CONTRIBUTIONS TO THE PMR

The PMR wave form becomes altered when a mydriatic is instilled for ERG recording. The next experiment is designed to assess the contribution of the pupillary light reflex to the PMR.

Procedure. The PMR was recorded with undilated pupils by the procedures of the first experiment. The cone and electrode were then removed and a mydriatic was instilled into the experimental eye. The electrode and cone were replaced, the fellow eye was stimulated, and responses of the experimental eye were recorded.

Results. The long-lasting positive component of the artefact (arrow in Fig. 3a) is abolished by mydriasis of the pupil (arrows in Fig. 3b). Therefore we conclude that this late, slow potential is a pupillary response to the light flash. These results and conclusions are identical to those of Pearlman,[5] based on his studies of the ERG c wave.

3. HABITUATION OF THE PMR

Repeated stimulus presentations diminished the amplitude of the PMR. The next experiment demonstrates that the amplitude reductions are the result of habituation rather than adaptation.

Procedure. Recordings were obtained simultaneously from the occluded and nonoccluded eyes. Stimulus flashes were presented every 3 seconds to the nonoccluded eye. Forty-five seconds after the flashes were terminated 2 additional flashes, 45 s apart, were presented.

Results. The ERG from the nonoccluded eye remained constant in amplitude, i.e., no changes in adaptation occurred. Fig. 4a illustrates the responses in the covered eye to 4 successive flashes, 3 s apart. The first response to the stimulus was the largest, the last the smallest. Fig. 4b shows the responses to the next 4 flashes of light. Aside from the late pupillary response, the wave form is almost completely

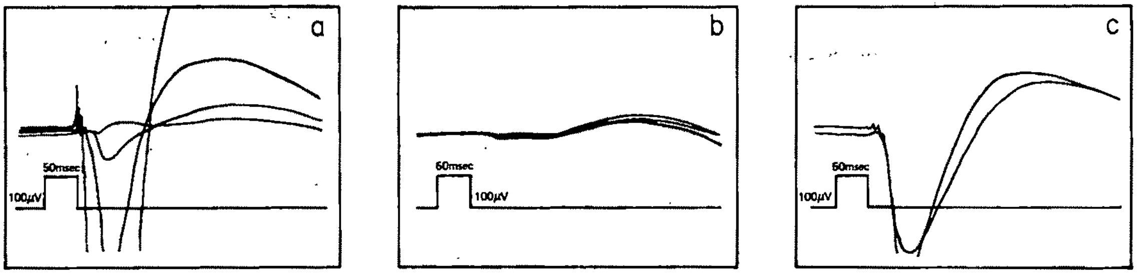

Fig. 4 *Habituation of the PMR.* (a). *Four PMRs, 3 s apart, recorded in standard fashion from one subject. The first response is the largest negative deflection, the second response is the second largest negative deflection, etc.* (b) *Four responses, 3 s apart, to the next 4 flashes of light show complete habituation of the negative wave of the PMR. The late positive wave is the pupillary reflex.* (c) *Return of the PMR, recorded 45 s after cessation of habituating stimulus. The 2 responses were recorded 45 s apart.*

abolished. Fig. 4c illustrates 2 responses, 45 s apart, recorded 45 s after the records shown in Fig. 4b. The PMR was again elicited.

The results of this experiment indicate that the PMR becomes habituated with repeated stimulation, despite no apparent changes in retinal adaptation. This habituation presumably is under CNS control.

4. CONDITIONED SUPPRESSION OF THE PMR

Recent studies have shown that the blink reflex to tactile stimulation can be suppressed by auditory stimuli.[6 7] If the PMR arises by way of a noncortical pathway, as suggested by its short latency, it should not be possible to condition it to a cross-modal stimulus, although response modification by conditioned suppression may be possible.

Procedure. The PMR was recorded from the occluded eye as described previously. A 50 ms tone was presented, instead of the light, in order to determine whether the PMR could be elicited solely by the tone. The tone then was paired with the light flash, preceding the light by 150 ms, and presented every 3 s for a period of 15 min. After this training period the tone alone, then the flash alone, and then the tone followed by the flash were delivered to determine the effects of conditioning.

Results. Fig. 5a shows that prior to conditioning the tone alone did not elicit a PMR. Fig. 5b illustrates that the tone alone also failed to elicit a PMR after conditioning. Thus the PMR could not be conditioned to the cross-modal stimulus. Fig. 5c is the response elicited by light alone after conditioning

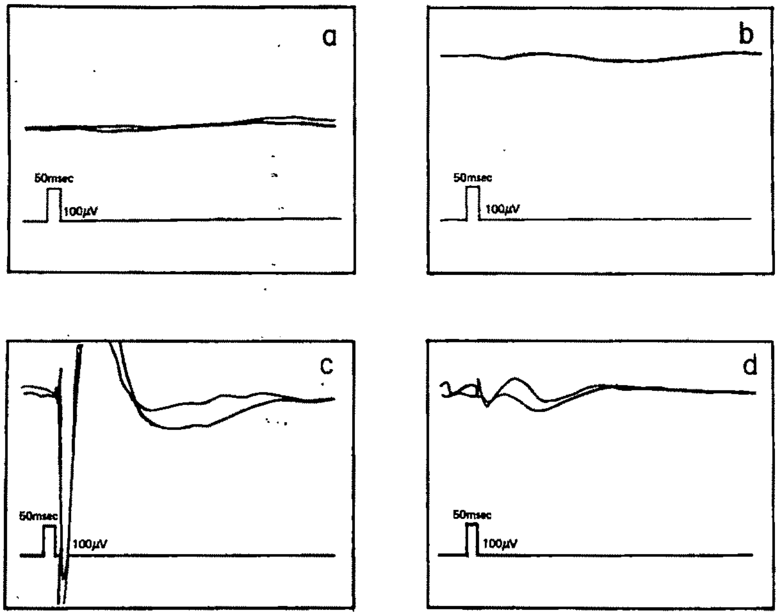

Fig. 5 *Conditioned suppression of the PMR by an auditory stimulus. The PMR was recorded in the standard manner.* (a) *Before conditioning, no reflex was elicited by a 50 ms tone.* (b) *The tone was paired with (presented 150 ms before) a flash of light for about 15 min. After this conditioning no response was elicited by the tone alone. A large-amplitude PMR was elicited by the light only* (c), *but not when both tone and flash were presented* (d). *Presence of the tone ahead of the flash suppressed the reflex.*

trials, and Fig. 5d is the response to the light paired with the tone. Figs. 5c and 5d show that, after conditioning, the tone suppressed the PMR, i.e., the PMR is dramatically reduced in amplitude when the light flash is paired with the tone.

These data indicate that the PMR probably has a subcortical origin but can be suppressed by the cortex. In contrast, pupillary reflexes cannot be suppressed in this manner. Furthermore PMR habituation and suppression rule out any putative roles of electrotonic spread of excitation[8] as the source of the PMR.

5. CONTRIBUTION OF THE ORBICULARIS TO THE PMR

Karpe[3] attributed artefacts such as the PMR to dazzle reflex eyelid movements. Electroretinographers are aware that from time to time 'blinks' occur in ERG records. Bickford[2] suggested that an eye movement rather than a blink is responsible for variations in the ERG. However, in a study of blink reflexes Miles[4] noted that eye movements accompany all blinks, actual or aborted.

Rushworth[9] measured the latencies of over 600 light-induced blink reflexes in 20 patients and found a mean near 60 ms. As we found for the PMR, he observed that the blink could be elicited in the contralateral eye, that it could show habituation, and that it did not become conditioned to an auditory stimulus. The next experiment was designed to determine the contribution of a blink to the PMR.

Procedure. A modified Van Lint lid block was performed on one of the authors with 10 ml of a 50:50 mixture of 2% lignocaine and 0·75% bupivacaine, with added hyaluronic acid. The subcutaneous tissues were infiltrated with the anaesthetic solution surrounding the orbital rim and extending back 4 cm toward the tragus of the ear. This lid block was clinically complete in paralysing the orbicularis muscle within 15 min, resulting in the subject's inability to close the eye, and lasting for about 3 hours.

Prior to the lid block ERG electrodes were placed in both the occluded and nonoccluded eyes, and the ERG and PMR were simultaneously recorded. this procedure was repeated after the orbicularis of the occluded eye was completely paralysed by the lid block.

Results. Fig. 6a shows that the PMR was present in both eyes prior to the lid block. The top trace is the PMR superimposed on the ERG from the unoccluded eye. The bottom trace is the PMR from the occluded, experimental eye. Note that the PMR is consensual.

Fig. 6b illustrates the PMR after the orbicularis muscle of the occluded eye is paralysed. As before, the PMR was elicited in the nonoccluded eye (top trace). As seen in the bottom trace, paralysis of the orbicularis eliminates the spiking and the initial negative potential of the PMR. However, a small corneal-positive potential remains.

These data indicate that the major portion of the initial corneal-negative wave form of the PMR can be attributed to contraction of the orbicularis.

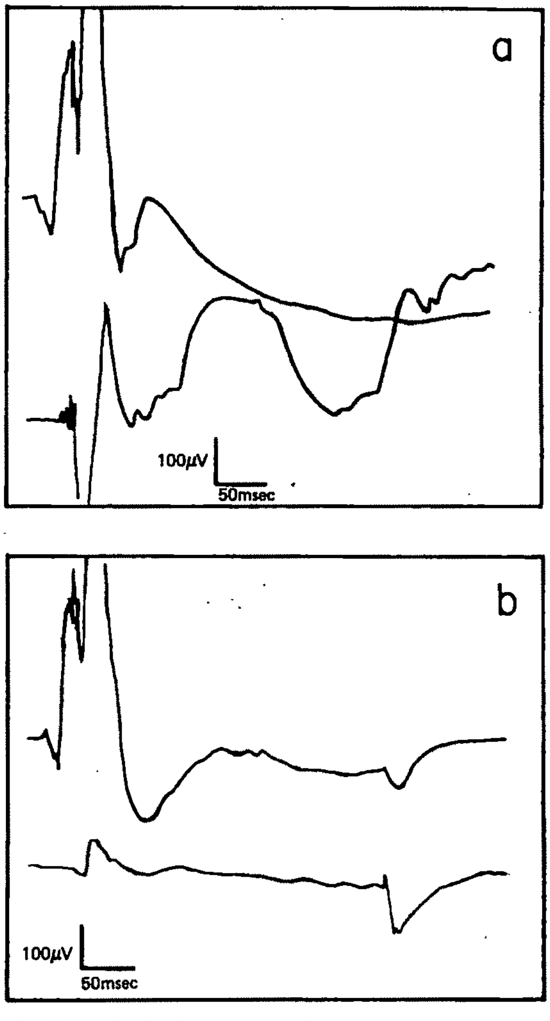

Fig. 6 *Role of orbicularis muscle contraction in the PMR. Electrodes were placed on both eyes, and one eye was occluded from the light.* (a) *The top trace shows the ERG and PMR recorded from one eye, and the bottom trace shows just the PMR recorded from the occluded fellow eye.* (b) *A modified unilateral Van Lint lid block was then administered to the covered eye. Twenty minutes later the light-elicited responses were again recorded from both eyes under the same conditions. Most of the PMR was eliminated by the lid block (lower trace), indicating substantial contributions from the orbicularis muscle.*

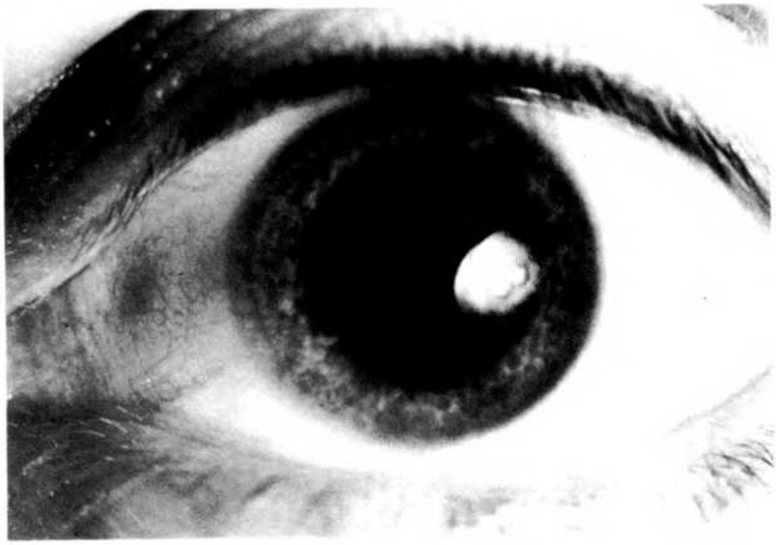

Fig. 7 *Double-exposure photograph showing small eye and eyelid movements. Photograph was taken in a dark room with the camera shutter held open. The light source was a strobe, triggered to double flash with an interflash interval of 120 ms. Note the 2 displaced corneal reflections from the strobe and the displaced images of the scleral vasculature and eyelashes.*

Furthermore, because the initial spiking was eliminated, we conclude that it too may be attributed to the orbicularis. This latter conclusion is in agreement with Kennard and Glaser,[10] who attributed spiking in blink reflex records to nervous innervation of the orbicularis muscle.

6. THE ROLE OF EYE MOVEMENTS IN THE PMR

The residual response in Fig. 6b may be due to a small eye movement. This hypothesis is consistent with the finding by Miles[4] that all blinks, whether actual or aborted, are accompanied by eye movements. The following experiments examined this possibility.

Procedure. We recorded reflex movement of the eye by photographing the eye before and during the PMR. In a dark room a camera was focused on the subject's eye, and the shutter was opened. A double strobe flash was then delivered to the subject. The interval between flashes was 120 ms, which is roughly the implicit time of the PMR.

An accurate determination of the amplitude and direction of this eye movement was established by the following procedure. A Burian-Allen bipolar ERG electrode was placed on one eye to record the presence of the PMR. The other eye contained a scleral eye coil which, when the subject was placed in a magnetic field, could record eye movements with a resolution of less than 30 minutes of arc (for methods, see Robinson[11] and Collewijn *et al.*[12]). A strobe flash was used as the stimulus.

Results. The double-exposed photographs showed small movements of the eyelid and eye in the 3 subjects tested. Fig. 7 is a typical photograph from one subject. Note the 2 displaced corneal reflections from the strobe, and also displaced images of the scleral vasculature and the eyelashes. This observation supports the hypothesis that the remnant of reflex after the lid block can be attributed to eye movement.

Data from the scleral coil eye movement recordings are shown in Fig. 8. Figs. 8a and b are records obtained during the same light flash. Fig. 8a is the record from the ERG electrode, which shows that a PMR having a latency of 55 ms (arrow) occurred in response to the light flash. Record 8b from the eye coil shows an eye movement with a latency of 65 ms, occurring downwards and medially. Eye movements from the 2 subjects tested had amplitudes ranging from 1·5° to 3·5°.

These data show that eye movements occur in conjunction with reflex blinks during a PMR. The eye movements have slightly longer latencies and apparently produce smaller potentials than eyelid movements.

Clinical ERG Interpretations and the PMR

Important considerations for assessing the impact of the PMR on ERG interpretation must include: (1) the timing of the PMR in relation to the various components of the ERG, and (2) the shape of the PMR wave form and how it may distort or mimic the ERG wave form. These aspects of the PMR are explored in the next set of experiments. Also, a brief study comparing the propensity of several popular ERG electrode types to record the PMR is described.

7. INTENSITY-RESPONSE CHARACTERISTICS OF THE PMR

We obtained an intensity-response function for the

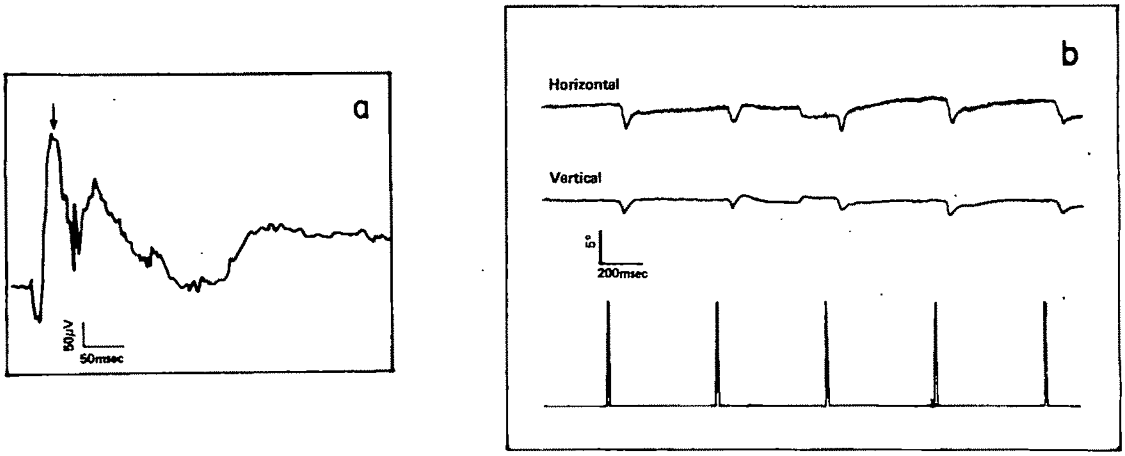

Fig. 8 *Extent of eye movements in a PMR elicited by a strobe flash were measured by a scleral eye coil.*[12] (a) *Record from a standard ERG electrode which was placed on the fellow eye to record the presence of the PMR. The arrow points to PMR onset.* (b) *Eye movement recordings. Calibrations were obtained by saccadic pursuit of stepwise horizontal or vertical displacements of a fixation spot. Horizontal and vertical components of the light-elicited reflex eye movement were recorded on 2 separate channels of a pen writer. The horizontal component (up=rightward movement) of the eye movement measured in the subject's right eye has a latency of about 65 ms and an average amplitude of about 3° in this subject. The vertical component (up=upward movement) occurs simultaneously with the horizontal component and has an average amplitude of about 2° in this subject. Consequently the direction of the eye movement was toward 7 o'clock (downwards and medial) with an amplitude of about 3·5°.*

PMR in order to determine how the latency and amplitude related to stimulus strength.

Procedure. The PMR was recorded from the occluded eye by the procedures described above. Stimuli of increasing intensity, covering a range of 3 log units, were presented to the unoccluded eye. Results were compared with ERG records obtained at an earlier date from the same subject by means of the same stimuli and order of stimulus presentation.

Results. We found that the amplitude of the PMR does not depend on stimulus strength in any predictable fashion; amplitude depends mainly on the state of habituation. However, there is a PMR threshold, which varied between observers. Latency on the other hand decreased slightly (from 67 to 56 ms) over a 3 log-unit increase of intensity (Fig. 9). To determine the effect of PMR latency change (or lack of it) on ERG interpretation, the implicit times (time from stimulus onset to peak of the wavelet) of ERG b waves, obtained under the same stimulus conditions as the PMR, were plotted along with the PMR data. (The b wave implicit time was selected for comparison because the appearance of the b wave in patients usually forms the basis for ERG evaluation.) As seen in Fig. 9, the graphs of the 2 functions cross at 57 ms. For example, for this subject at all but the 2 highest intensities the PMR starts at a time before the b wave reaches its peak amplitude.

The effect of PMR on ERGs elicited by a low-intensity ($-2{\cdot}16$ log cd. s. m^{-2}) and a high-intensity ($-0{\cdot}26$ log cd. s. m^{-2}) stimulus is shown in Figs. 10, 11, and 12. Fig. 10 shows a maximal-amplitude ERG (*a*) and an ERG elicited with about 2 log units less

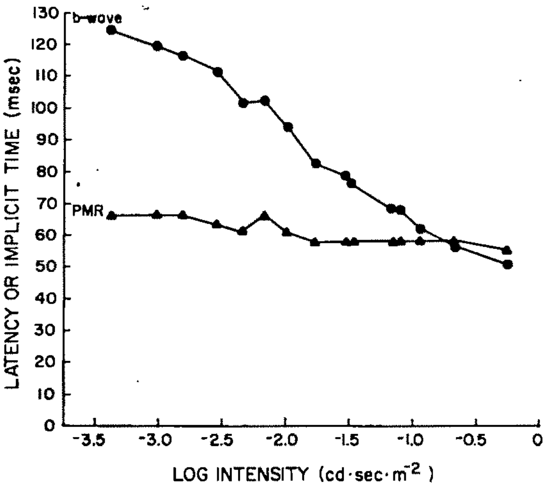

Fig. 9 *Latency of the PMR and b wave implicit time as a function of intensity in log cd. sec. m^{-2}. Over a 3-log unit range of intensities the b wave implicit time markedly decreased, while the PMR latency showed only a slight reduction. The graphs of the 2 functions cross at approximately $-0{\cdot}7$ log cd. s. m^{-2} (57 ms), indicating that for most of the dynamic range of the b wave, the PMR will occur before the b wave peak.*

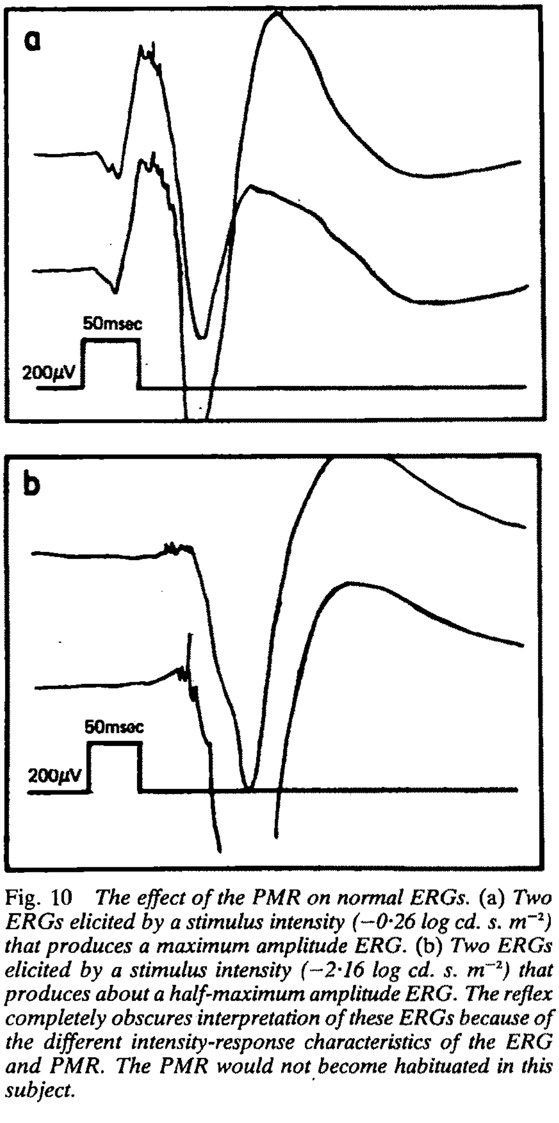

Fig. 10 *The effect of the PMR on normal ERGs.* (a) *Two ERGs elicited by a stimulus intensity ($-0{\cdot}26$ log cd. s. m^{-2}) that produces a maximum amplitude ERG.* (b) *Two ERGs elicited by a stimulus intensity ($-2{\cdot}16$ log cd. s. m^{-2}) that produces about a half-maximum amplitude ERG. The reflex completely obscures interpretation of these ERGs because of the different intensity-response characteristics of the ERG and PMR. The PMR would not become habituated in this subject.*

intensity (*b*) from a normal volunteer. In this case the reflex occurs slightly faster than for the subject reported above (Fig. 9), making measurement of the amplitude of the maximal-amplitude ERG difficult, and measurement of the amplitude of the lower-amplitude ERG impossible (because the implicit time of the b wave increases as the stimulus intensity decreases).

Fig. 11a illustrates ERGs from another subject in response to a light intensity that evoked a maximal amplitude ERG. Repeated, predictable deliveries of the stimulus habituated the reflex and eventually produced a totally time-locked b wave response (Figs. 11b and c). Fig. 12a illustrates 2 ERGs from the same subject, elicited by light of about 2 log units less intensity than that in Fig. 11. Note how the apparent implicit times of the b waves changes with habituation of the PMR. Fig. 12b is a record of 10 consecutive responses to the same conditions after habituation of the reflex was achieved.

8. POLARITY OF THE PMR

We noticed in some cases that the polarity of the initial negative deflection of the PMR was reversed. The polarity of the pupillary response, however, remained corneal-positive in these individuals. PMRs of inverted polarity closely resembled ERGs of normal amplitude and delayed timing. The polarity change could be attributed to electrode position in relation to the standing field potential of the eye. If the initial position of the electrode was at the most positive pole of the eye, then any movements of the electrode or the eye would be expected to produce a negative deflection. In contrast, if the electrode's initial position was away from the most positive pole, then movements bringing the electrode position closer to the pole would be expected to produce a positive response. To test these possibilities the effect of initial ERG electrode position on the polarity of the response of voluntary eye movements was determined in the next experiment.

Procedure. The relative position of the electrode was changed by instructing the subject either to fixate a red LED directly in front of him, allowing the examiner to obtain central positioning of the contact lens on the cornea, or to fixate about 15° above or below the LED, with his head still orientated directly forwards, allowing the examiner to obtain eccentric positioning of the contact lens in relation to the centre of the cornea. The subject was then instructed to execute a voluntary eye movement—either up, down, left, or right—when cued by a flash of light.

Results. A corneal-negative potential was recorded when the 2 subjects, fixating centrally, looked up. A similar potential was recorded when the subject directed his fixation from centre, either downwards or to the left or right. The potential was corneal-positive when the subject fixated eccentrically and moved his gaze to the centrally located LED. Thus, depending on the position of the contact lens in relation to the center of the cornea, normal eye blinks and movements of the eye under the electrode during ERG recording could result in either corneal-positive or corneal-negative PMRs.

Small corneal-positive PMRs, regardless of their origin, which occur in patients who have extinguished or severely reduced ERGs can easily be misinterpreted as being ERGs, because, as Karpe demonstrated, these PMRs can closely resemble retinal

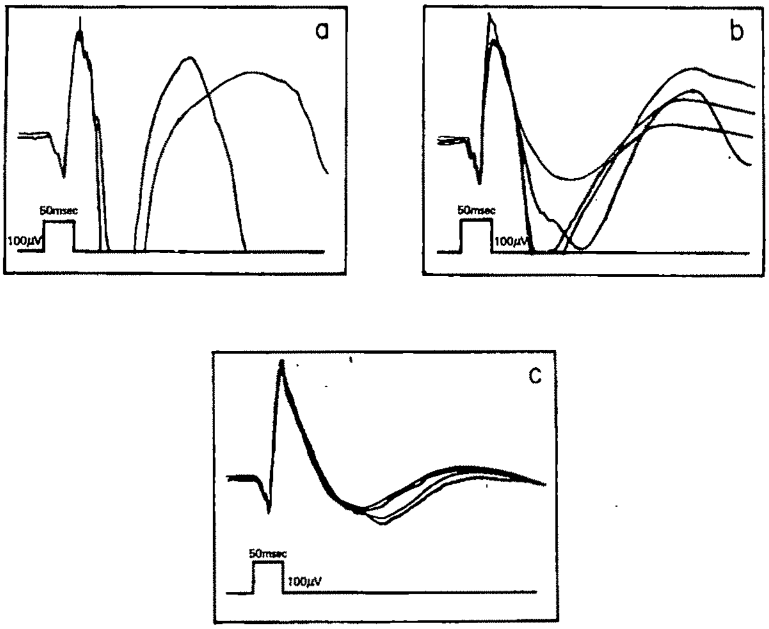

Fig. 11 *The effect of habituation on the maximal amplitude ERG.* (a) *Two ERGs recorded from a normal subject. Note how the ERG wave form breaks down at the peak of the b wave where the PMR begins.* (b) *Recorded during habituation, these 4 ERGs begin to show less variation in wave form.* (c) *The next 4 ERGs recorded are virtually superimposable because of the nearly total habituation of the PMR.*

potentials. The epitome of this imitation is the clinical ERG shown in Fig. 13a, recorded from a patient with retinitis pigmentosa (RP). Because the response would not become habituated, it was not until the eye with the electrode was occluded and the fellow eye was stimulated (Fig. 13b) that the identity of the potential as a PMR was conclusively established. Note how closely this PMR resembles an ERG of normal amplitude but delayed timing.

Distortion of the ERG by the PMR has been observed similarly with various other patients. For example, the top trace of Fig. 14 shows the ERG record obtained from another RP patient. The larger, slower potential could be interpreted as a delayed rod b wave, thus giving rise to abnormal splitting of rod and cone components. However, in this case habituation eliminated the PMR contribution to the potential, and the patient's actual ERG is shown in the middle trace of Fig. 14.

9. EFFECT OF ELECTRODE TYPE ON THE RECORDABILITY OF THE PMR

Several different types of electrodes are at present used to record the clinical ERG. We tested 3 of the

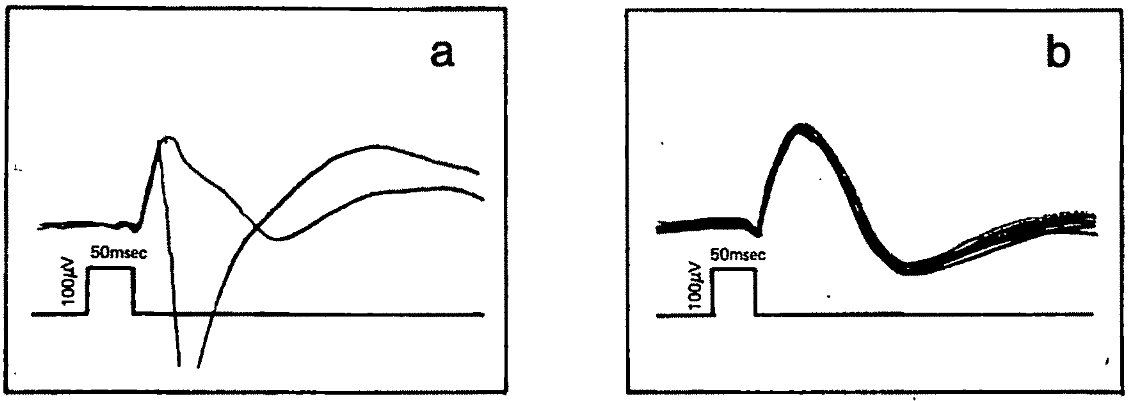

Fig. 12 *The effect of habituation on a half-maximum amplitude ERG.* (a) *Two ERGs recorded from a normal subject using the lower-intensity ($-2{\cdot}16$ og. cd. s. m^{-2}) stimulus. Note that the apparent implicit times of the b wave change with habituation of the PMR.* (b) *Ten consecutive ERGs, recorded 3 s apart, after habituation of the PMR. The waveform is now totally time-locked to the stimulus.*

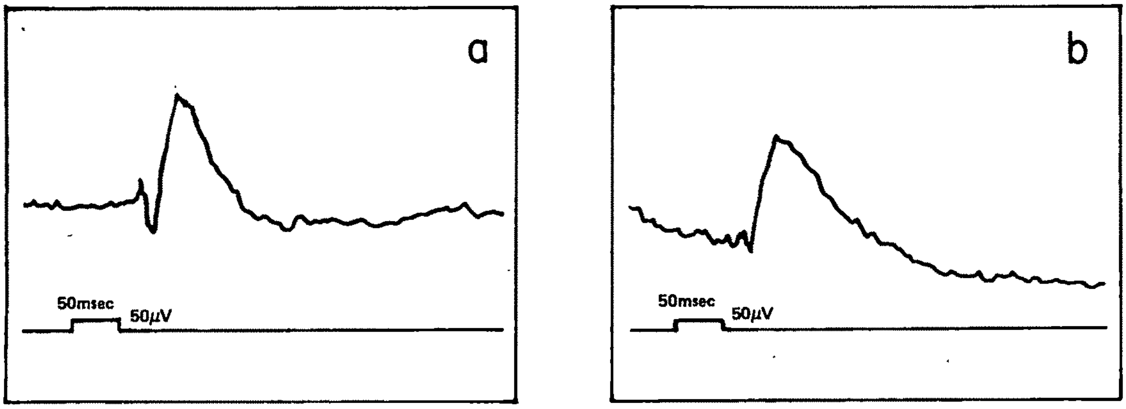

Fig. 13 *The PMR in retinitis pigmentosa (RP).* (a) *This record was obtained during ERG testing of an RP patient. The waveform resembles a normal amplitude ERG delayed in implicit time.* (b) *The eye containing the electrode was occluded, and the fellow eye was stimulated. Records obtained in this manner show that the waveform is artefactual.*

most popular electrodes—the Burian-Allen bipolar electrode, the Burian-Allen monopolar electrode, and the gold foil electrode—comparing their sensitivity to recording the PMR.

Procedure. Because the Burian-Allen bipolar electrode was used throughout this study it became a reference in this experiment, recording the PMR in one eye while the gold foil or monopolar electrode recorded the PMR simultaneously in the occluded fellow eye. This manipulation permitted us to determine when the PMR was present and also to evaluate its recordability after habituation. The control experiments were performed, in which both eyes were occluded, to ensure that no light reached the experimental eye.

Results. The monopolar electrode recorded a lower amplitude PMR than was recorded by the bipolar electrode. This reduction in amplitude of the PMR appears to be mainly due to a reduction in recordability of the lid component; no extremely large PMRs were noted, and onset spiking was absent from most records. The main difference between the 2 electrodes is that the indifferent electrode is located in the speculum of the bipolar electrode, whereas it is placed on the patient's forehead for the monopolar electrode. Although the amplitude of the PMR

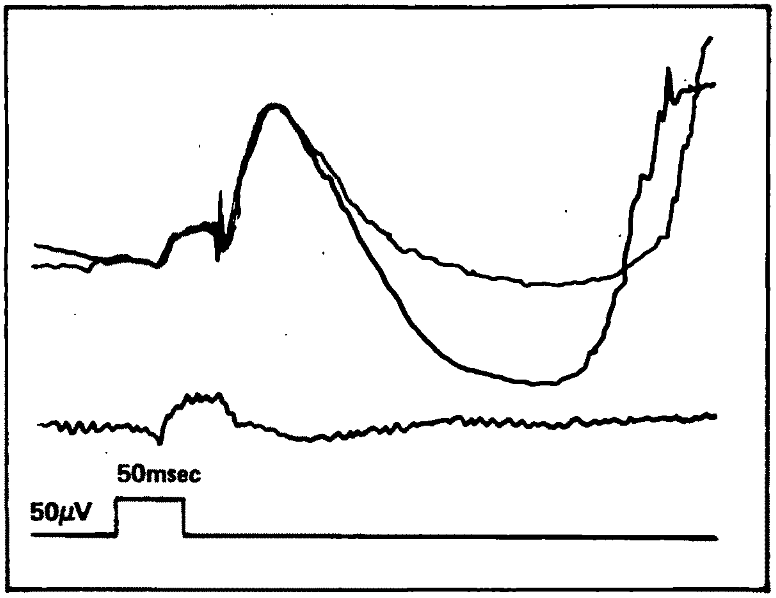

Fig. 14 *The PMR in RP. The top trace shows 2 ERG traces obtained from an RP patient during standard ERG testing. The larger, slower potential could be interpreted as a delayed rod b wave, thus giving rise to abnormal splitting of rod and cone components. Habituation in this case eliminated the PMR and revealed the patient's actual ERG (middle trace).*

recorded by the monopolar electrode was reduced, the response often closely resembled a delayed ERG.

The gold foil electrode was very sensitive to recording the PMR, possibly because it touches the lower lid, and a strong medial movement of the lower lid occurs during actual or aborted blinks.[10] The size of the PMR relative to that recorded with the bipolar electrode was quite variable during different sessions. This variability probably can be attributed to variable placement of the gold foil electrode and repositioning of the electrode by blinks.

Very little habituation was observed during testing of either the monopolar or gold foil electrode, despite habituation observed in the fellow eye with the bipolar electrode. In the case of the monopolar electrode lack of habituation may be due to the fact that the PMR recorded by this electrode was already quite small and may have mainly been due to the reflex eye movement. It is possible that the blink was becoming habituated, but the eye movement was not. In the case of the gold foil electrode even minor movements of the lower lid may have produced a sufficiently large response as to obscure signs of habituation.

In contrast it appears that the PMR cannot be recorded with the Henkes electrode. Van Norren (personal communication) indicated that he replicated the main experiments described here using the Henkes electrode, and when the experimental eye was occluded and the fellow eye stimulated no PMR could be recorded. Van Norren's failure to record the PMR probably can be attributed to the fact that the Henkes electrode is held on the cornea by a negative pressure; consequently the electrode moves with the eye and probably is not displaced by blinks.

Discussion

The present study has confirmed and described more fully an artefact that exists in the clinically recorded ERG. This artefact is a photomyoclonic reflex, consisting largely of eye lid movements and to a lesser extent eye movements. The mean latency of the PMR is approximately 59 ms.

It is important to recognise the appearance of the PMR in ERG records, because it can interfere with the recording and interpretation of both the amplitude and the latency of the ERG. The eyelid movement reflex can be habituated by regular, repeated, predictable stimulus presentations in some but not all subjects, and habituation, when it occurs, may occur to a different extent among various subjects. The eye movement contribution to the reflex does not appear to become habituated as easily, and may thus subtly affect interpretation of low-amplitude or nonrecordable ERGs. Partially habituated lid movements may also insidiously interfere with ERG interpretation, especially if the polarity of the potential is corneal-positive.

Burian-Allen bipolar and gold foil electrodes are more susceptible to recording the artefact, the former because of the placement of the indifferent electrode in the speculum, the latter because it rests on the lower lid, which moves medially with every actual or attempted blink.[10]

Because recording the PMR may be unavoidable with most electrodes, it is important to recognise this spurious wave form in ERG records. Often, but not always, identification of the PMR when using a bipolar electrode is facilitated by observation of spiking activity at the onset of the reflex.

This work was supported by research and core facility grants EY-01791 and EY-01765 from the National Eye Institute, and by a Research Center grant from the National Retinitis Pigmentosa Foundation.

We thank F. W. Fitzke, D. Guyton, A. Lasker, C. Perry, and D. Robinson for technical advice and assistance, D. Andrews and D. Finkelstein for comments on the manuscript, G. Fishman of the University of Illinois Eye and Ear Infirmary for the loan of the monopolar electrode, and D. van Norren of the Institute for Perception in Soesterberg, the Netherlands, for permitting us to cite his unpublished study.

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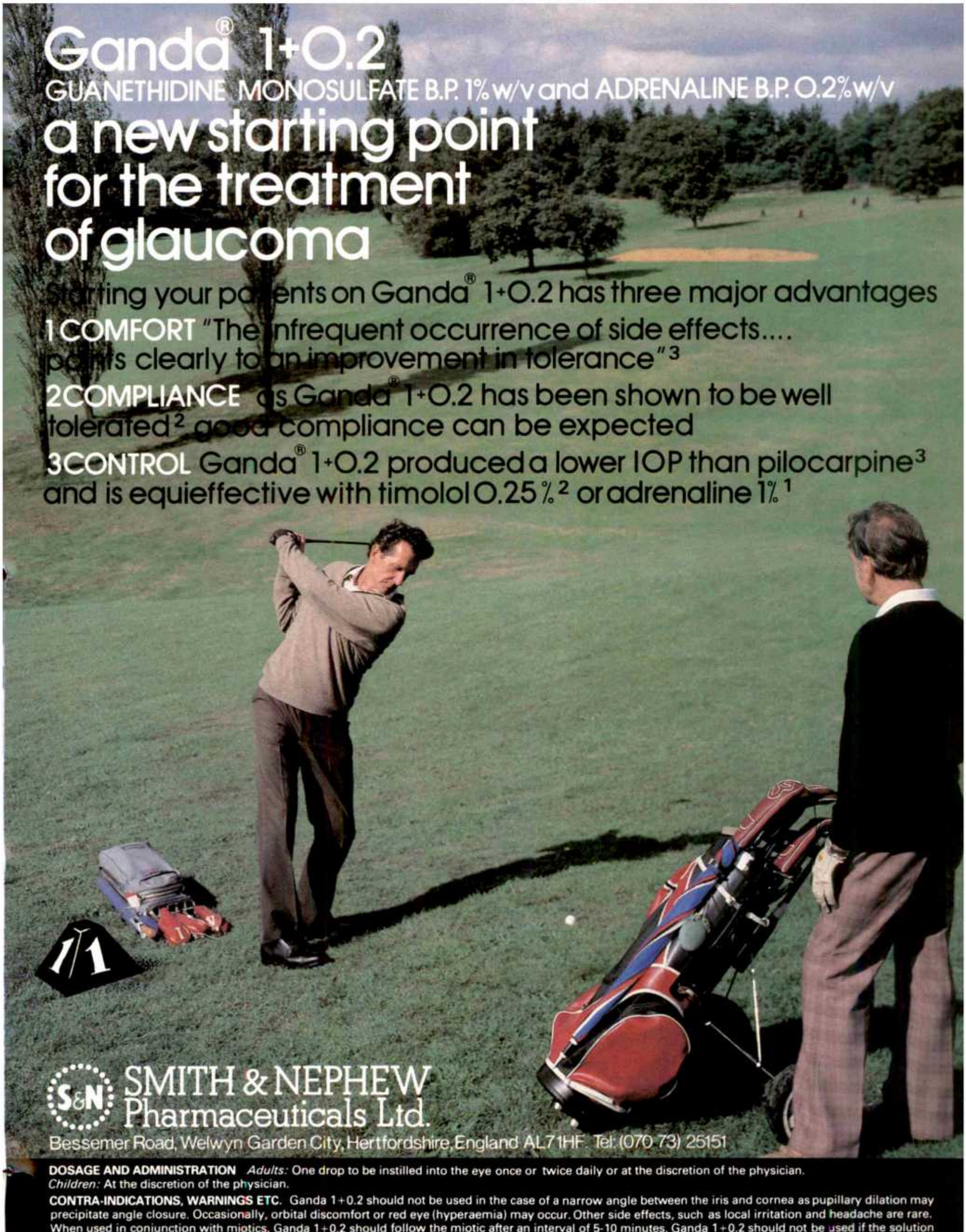

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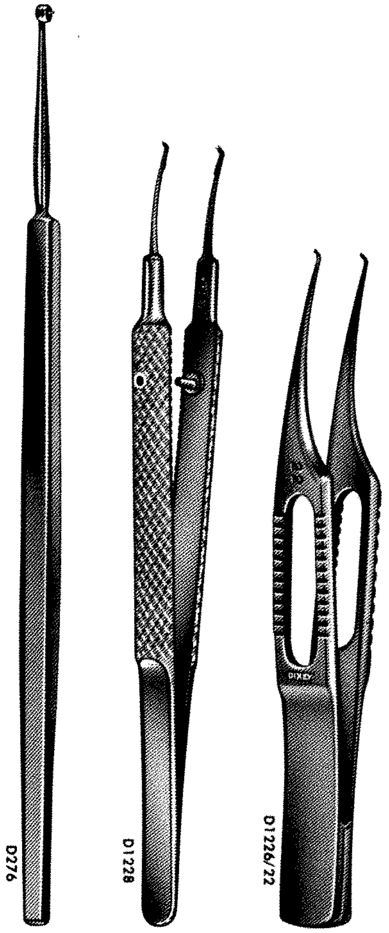

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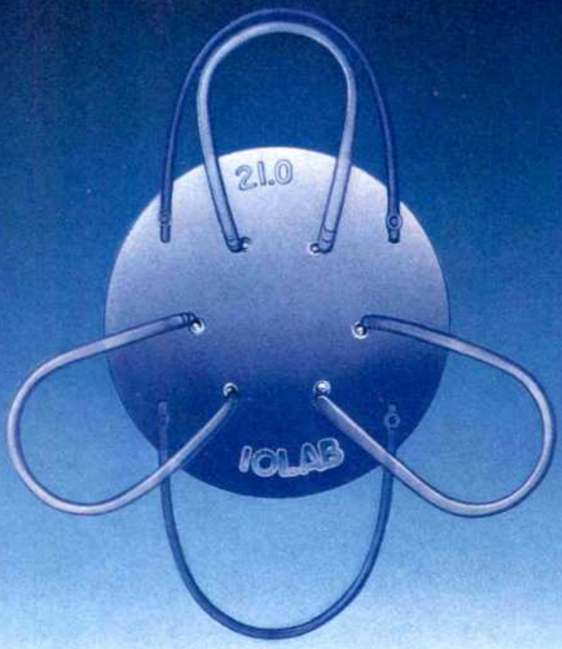

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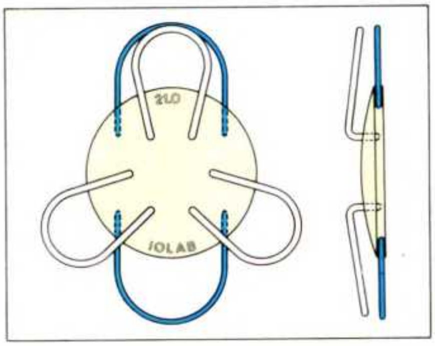

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British Journal of Ophthalmology, 1982, **66**, 379–381

The inverse electro-oculogram

BERNARD H. DOFT, STEPHEN A. BURNS, AND ANN ELSNER

From the Department of Ophthalmology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

SUMMARY An electro-oculogram ratio of less than one was found to be caused by limited ocular excursions under photopic conditions in a patient with a rod-cone dystrophy. Because this inverse electro-oculogram ratio was not caused by a decrease in standing potential under photopic conditions, it should be considered an artefact.

The electro-oculogram light-to-dark ratio is the ratio of the standing ocular potential under light-adapted conditions to that under dark-adapted conditions. Normally the standing potential increases under photopic conditions. François *et al.*[1] theoretically defined the opposite situation, a decrease in standing potential under photopic conditions, as an inverse electro-oculogram. However, he did not describe any patients who met these criteria. In a single paragraph Kelsey[2] reported having seen patients with electro-oculogram ratios less than one. He attributed this to 'severe unilateral eye disease' but did not describe the specific circumstances or patients. This report describes a patient with an inverse electro-oculogram ratio.

Case report

A 31-year-old white female complained of decreasing vision for several years. Her optometrist had recorded a vision of 20/30 in both eyes at age 21 and 20/60 in both eyes at age 25. The patient felt her vision was worst during daylight, though poor at night, and she preferred twilight levels of illumination. One sister had night blindness and an unrecordable electroretinogram, and was diagnosed as having a rod-cone degeneration. Another sister had normal vision. Though both parents were deceased, the sisters suspected there had been parental consanguinity.

On examination the patient's visual acuity was 3/200 in the right eye and 20/200 in the left eye. The anterior segments, applanation tension, pupils, motility, and vitreous were normal. Fundus examination showed thinning of the retinal arteries, waxy pallor of the optic discs, and circumscribed areas of atrophy of the pigment epithelium in the macula in both eyes. Some perimacular pigment clumping was present.

Fluorescein angiography showed window defects in the pigment epithelium corresponding to the areas of atrophy seen clinically, as well as loss of choriocapillaris in these areas. Goldmann visual fields showed constriction of all isoptres, with large nasal scotomas in both eyes. The patient made 1045 errors on the Farnsworth-Munsell 100 hue test. The electroretinogram was extinguished under scotopic or photopic levels of illumination. Final dark-adaptation thresholds were assessed by the Tübingen perimeter with an 11 degree central target. The patient's final threshold with broad-band blue light was $-3{\cdot}86\ \log_{10}\text{cd/m}^2$ in the right eye, and $-3{\cdot}54\ \log_{10}$ in the left eye. These final thresholds were approximately 10 times less sensitive than results obtained in normal persons. Final thresholds for the sister with the known rod-cone degeneration were further reduced by a factor of 10.

An electro-oculogram was obtained by standard techniques,[3] with instructions to the patient at the beginning of this test sequentially to fixate alternatingly illuminated light-emitting diode target lights which were separated by 30 degrees. The electro-oculogram light-to-dark ratio was 0·32 in the right eye and 0·51 in the left eye (Fig. 1).

The patient was called back for repeat examination in an attempt to explain the unusual finding of an electro-oculogram ratio less than unity. With independent observation of eye position it was found that monocularly under scotopic conditions she could readily visualise both target lights. However, under photopic conditions she was unable to see one of the 2 target lights. When she was then verbally coached as to when the target light switched sides, the electro-oculogram light-to-dark ratio was found to be 2·33 in the right eye and 2·73 in the left eye (Fig. 2).

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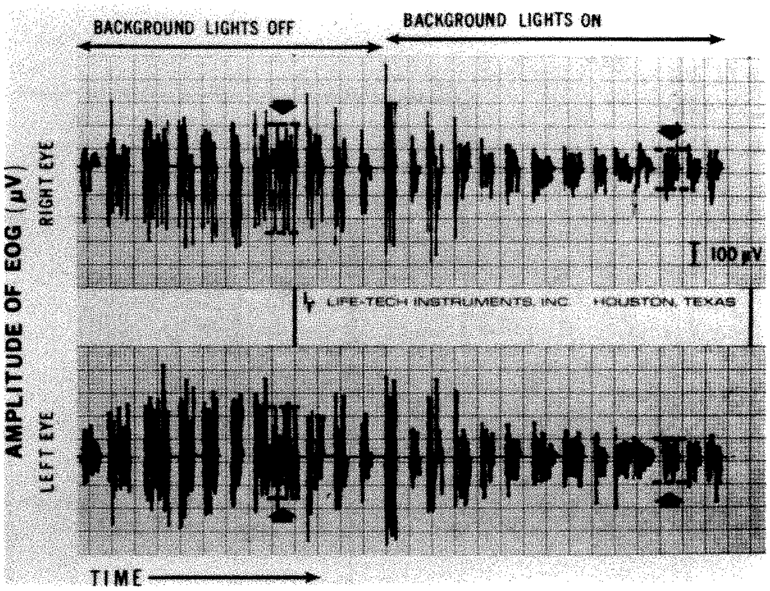

Fig. 1 *Electro-oculogram amplitudes recorded under light and dark conditions. Each response cluster represents approximately 15 seconds of recording. Recordings were obtained at one-minute intervals. Bold arrows indicate the responses used to calculate the electro-oculogram ratio.*

Discussion

The electro-oculogram is performed with the patient sequentially fixating targets separated by 30 degrees. Since the eye acts as a dipole, the electrical potential recorded depends on the amplitude of excursion the eye makes as it sequentially fixates these targets. For alternations of the electro-oculogram to reflect changes in standing potential the eye movements must be of constant amplitude under all recording conditions.

The patient described had a severe visual deficit, large scotomas, and progressive cone-rod degeneration. Under photopic conditions she had a difficult time seeing one of the light-emitting diode target lights. As the target light she visualised was turned off, she did not easily see the second target light. Therefore the amplitude of her ocular excursion was

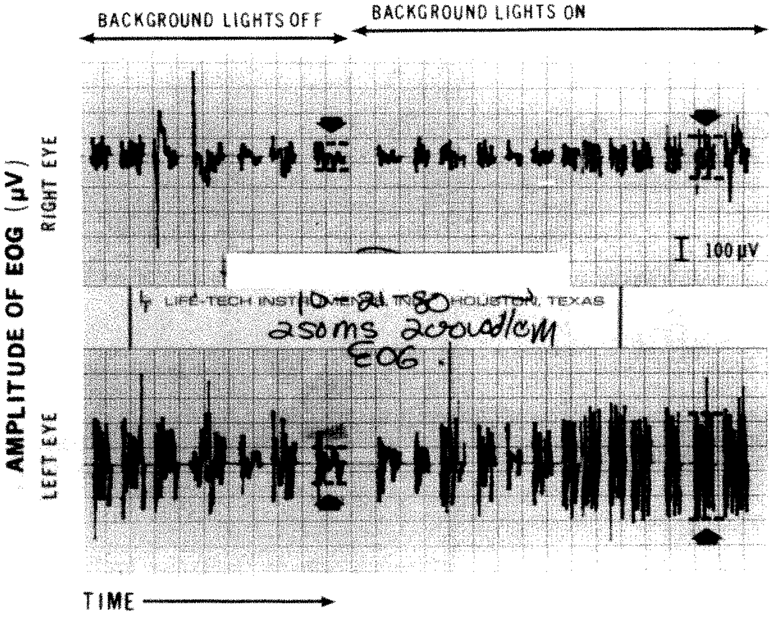

Fig. 2 *Electro-oculogram amplitudes recorded as in Fig. 1 except that the patient was verbally coached as to when to change fixation.*

decreased, resulting in the recording of only a small change in potential. Under scotopic conditions, however, she could see both target lights, and the amplitude of her ocular excursions was at least the full 30 degrees. We propose that it was the difference in the magnitude of ocular excursions between photopic and scotopic conditions that resulted in the appearance of an inverse electro-oculogram. Since the inverse electro-oculogram did not represent the physiological occurrence of a decrease in standing potential under photopic conditions, it cannot be considered representative. Indeed it is possible that the normal finding on the repeat electro-oculogram was also unrepresentative. On repeat testing the patient was verbally coached as to when to switch fixation. While unable to visualise one of the target lights under light-adapted conditions, she may have overcompensated, moving her eyes a larger angle than 30 degrees.

We stress the finding of an inverse electro-oculogram to emphasise the possibility of obtaining unrepresentative electro-oculogram responses when testing any patient who may have a pathological difference between light-adapted and dark-adapted visual thresholds. Independent monitoring of eye position and attention towards maintaining amplitudes of ocular excursion constant during electro-oculogram testing would prevent these misleading results from occurring.

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Visual evoked response in transient monocular visual loss

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From the [1]Eye Foundation Hospital, Department of Ophthalmology, University of Alabama, Birmingham, Alabama, and the [2]Bascom Palmer Eye Institute, Department of Ophthalmology, University of Miami, Miami, Florida, USA

SUMMARY The pattern-reversal visual evoked response (VER) was recorded in 2 patients during transient monocular visual reduction. In both cases the VER was initially abolished. With recovery of vision there was gradual return of amplitude over a 3- to 8-minute period, while latencies remained unchanged from preattack values. These findings are discussed with regard to current understanding of the origins of the VER and relevant aspects of retinal electrophysiology.

Amaurosis fugax typically is the result of retinal microembolisation, classically from occlusive disease of the extracranial carotid artery,[1] or from other sources.[2-6] Rarely, retinal vasospasm has been documented as a cause of transient visual loss.[1 7-9] We had the opportunity to record the visual evoked response (VER) during monocular loss and subsequent return of vision in 2 patients. While other aspects of these cases were described elsewhere,[8 9] the unique opportunity to record the VER prompted this report. To the best of our knowledge the VER has not been previously recorded during transient monocular visual reduction.

Materials and methods

During attacks of transient monocular visual loss the VER was obtained in different laboratories. Nevertheless the basic technique was similar, employing pattern-reversal stimulation with large checks (60′ to 80′ of arc) at low frequency (1-3 Hz), recording transient responses in each case.

Our first patient, wearing appropriate refractive error, was positioned 75 cm in front of a screen on to which was projected a high-contrast black-and-white checkerboard pattern. The entire pattern subtended 23° of central visual field with each individual square subtending 60′ of arc. The average luminance at the screen was 270 cd/m^2. Reversal was produced by angular oscillation (1·2 Hz) of a mirror. Occipital potentials were recorded with bipolar disc electrodes placed in the midline located 1 cm above the inion and at the vertex; an indifferent electrode was attached to the ear. The signal was passed through a preamplifier (Grass P-15) and a differential amplifier (Tektronix 3A9). Between 64 and 128 responses were averaged (Nicolet 1072 computer-averager) in at least 2 separate runs for each measurement. An observer monitored patient fixation throughout the course of VER testing. This technique produced a VER characterised by a small upward and larger downward deflection at approximately 100 ms. The negative component had the largest amplitude and was the most reliable complex. Latency was measured from the onset of the stimulus to the peak of this major negative component.

VER recordings for the second patient were obtained with a monopolar lead 1 cm above the inion and with a reference electrode at the mastoid process. The wave forms were recorded with a Nicolet CA-1000 system with television pattern generator. High-contrast black-and-white alternating check stimuli were presented at a reversal rate of 3 Hz, and 128 transient responses were averaged. At a distance of 4 feet (120 cm) each check subtended 80′ of arc, with the entire screen subtending 10° 42′ horizontally and 8° 30′ vertically. Patient fixation was monitored continuously by an observer. With this technique the VER was characterised by a small negative deflection and larger positive component at approximately 100 ms. Latency was measured from the onset of the stimulus to the peak of this major upward deflection.

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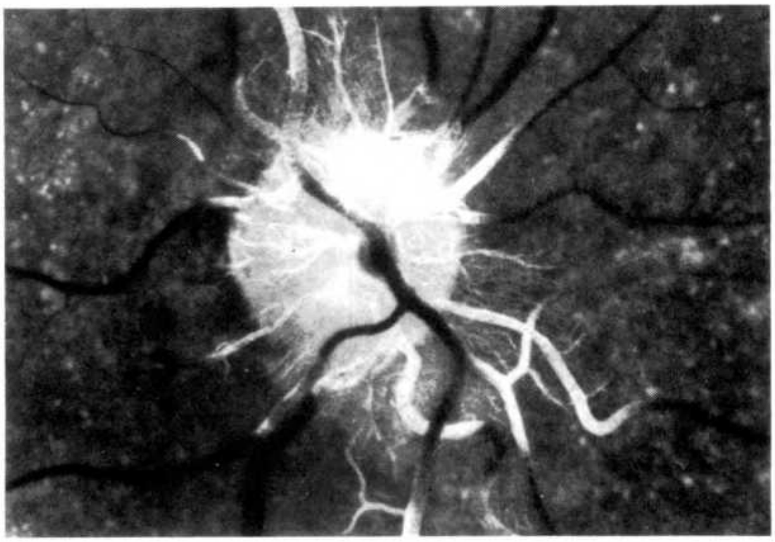

Fig. 1 *Case 1. Fluorescein angiography of right fundus, 55 seconds after onset of amaurotic fugax, demonstrates dye within vessels of the optic disc and segmental, incomplete filling of juxtapapillary retinal arterioles and veins. (Reprinted from Shaw et al.[8]).*

Case reports and results

CASE 1

A 23-year-old black woman had recurrent amaurosis fugax in her right eye for 3 months. When she was initially examined, her visual acuity was 20/20 in each eye. Visual field examination showed a superior arcuate scotoma in the left eye. Ophthalmoscopy revealed dilated arterioles and veins in the right eye. The left fundus showed areas of vascular sheathing suggestive of previous vasculitis. The remainder of the examination was normal.

During examination the patient had repeated amaurotic attacks in the right eye. Right vision was instantaneously reduced to no light perception, with a nonreactive, amaurotic right pupil. Ophthalmoscopy revealed narrowing of retinal arterioles and veins, cessation of retinal blood flow, segmentation of the blood columns, and optic disc pallor. During an episode of transient visual loss fluorescein angiography showed early filling of the right optic disc and peripapillary capillaries, but fluorescein dye was not seen in the retinal arterioles until 30 seconds after injection (Fig. 1). The patient was found to have both SC haemoglobinopathy and systemic lupus erythematosus. After treatment with prednisone the amaurotic attacks abruptly subsided. The patient has remained asymptomatic.

VER was obtained at the onset of amaurosis fugax, and after 2, 5, 8, and 11 minutes (Fig. 2). At the onset of the attack no VER was recordable, and with return of retinal perfusion the VER amplitude gradually increased over a 5–8-minute period. In contrast, as VER amplitudes returned, latencies were unchanged, measuring 94 ms (normal: 98±6 ms).

CASE 2

Four days prior to examination a 48-year-old man reported the onset of repeated episodes of 'almost

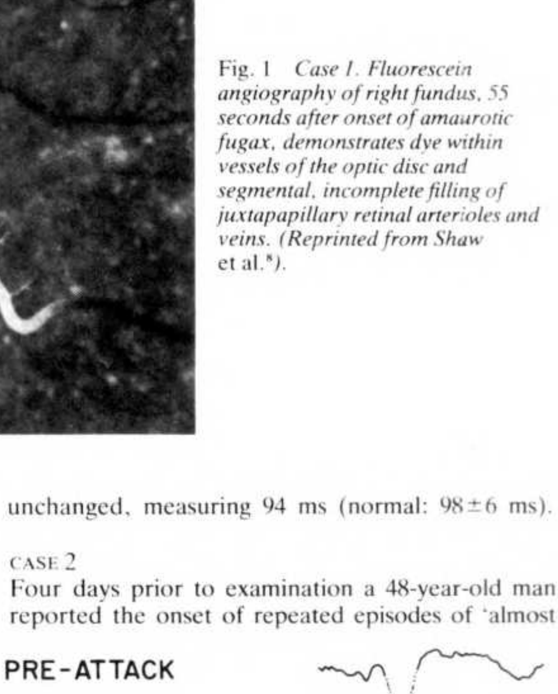

Fig. 2 *Case 1. Serial recordings of pattern-reversal VER during an attack of amaurosis fugax on the right due to spasm of the central retinal artery.*

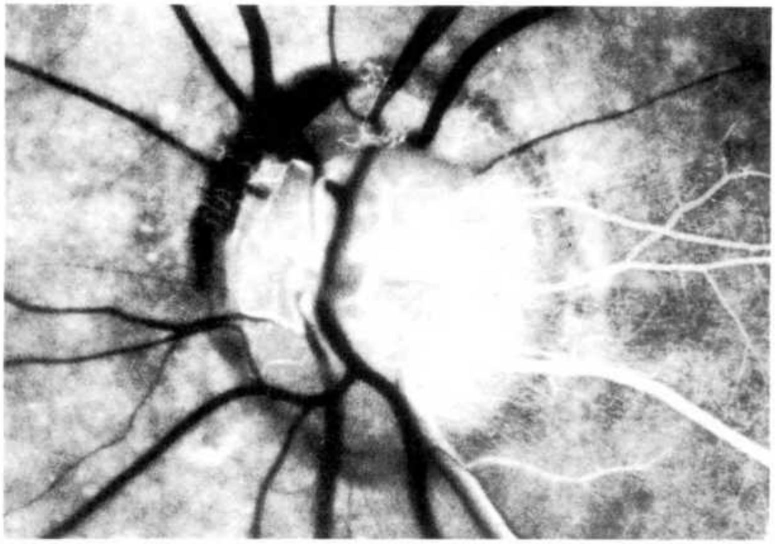

Fig. 3 *Case 2. Fluorescein angiography of the left eye 8 seconds after the onset of ocular migraine reveals filling of retinal vessels only inferotemporally. The remainder of the vessels filled approximately 30 seconds later. (Reprinted from Kline and Kelly[9]).*

total blindness' of the left eye lasting about 2 minutes. During these episodes he experienced progressive loss of peripheral visual field but maintained a small portion of central visual field, which he described as 'shaped like a leaf.' The patient had experienced classic cluster headaches for the past 25 years but none in the previous 6 months. There was no family history of migraine. While he was asymptomatic, neuro-ophthalmological testing was entirely normal, including funduscopic examination.

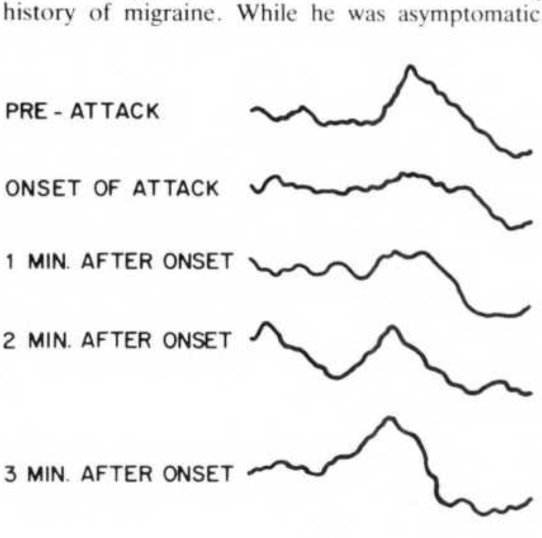

Fig. 4 *Case 2. Serial recordings of pattern-reversal VER during an episode of transient visual reduction of the left eye due to ocular migraine.*

While he was in hospital the monocular attacks of visual reduction, each lasting approximately 2 minutes, were studied in detail. The patient maintained visual acuity of 20/30 on the left, and a small central island of visual field. During the attacks the retinal veins narrowed. There was delay in the appearance of fluorescein dye in branches of the central retinal artery yet prompt filling of 2 cilioretinal vessels (Fig. 3). Haematological and cardiac investigations, including echocardiography, gave normal results, and no abnormalities were found on carotid angiography. Diagnosed as having ocular migraine, the patient was placed on propranolol, with prompt cessation of visual symptoms.

As seen in Fig. 4, at the onset of the attack of ocular migraine the VER was abolished. While amplitude returned over a 2–3-minute period, the latencies (102 ms) were essentially unchanged from preattack values (normal: 99 ms ± 7).

Discussion

The series of electrical and electrochemical events that leads to the elaboration of the VER begins in the photoreceptors of the retina and culiminates in the occipital cortex. Pattern-reversal VER has been found to show a more consistent waveform and to be more sensitive in detecting lesions of the visual pathways than has flash response.[10] In the assessment of afferent input to the visual cortex pattern-reversal VER has been studied in a variety of diseases of the optic nerve, including optic neuritis,[11] ischaemic optic neuropathy,[12 13] toxic amblyopia,[14] glaucoma,[15] and compressive optic neuropathy.[16] Comparison of amplitude and latency abnormalities has at times distinguished among such optic nerve diseases. For example, in the acute phase of demyelinative optic neuritis the amplitude of the pattern-reversal VER is reduced, and it returns to normal with clinical recovery, while characteristically prolonged latency remains.[11] However, in many instances it is difficult to separate the relative contribution of axonal degeneration and demyelination when VER abnormalities occur.

The 2 cases presented here provide an opportunity to examine selective impairment of axonal transmission within the optic nerve without disturbance of myelin sheaths. The central retinal artery is the sole vascular supply of the inner retinal layers (ganglion cells, inner plexiform layer, inner nuclear layer).[17] With temporary interruption of blood flow, inner retinal activity ceases and no VER is generated. With resumption of blood flow there is progressive increases in retinal neuronal function, and VER amplitude gradually returns (Figs. 2 and 4). But with gradual return of inner retinal function there is nevertheless a constant value for VER latency.

Investigations into the genesis of the VER have dealt with contributions from striate (area 17) and extrastriate (areas 18 and 19) cortex.[18–20] An understanding of the relationship between the VER and underlying neural events is far from complete. The only study dealing with the origin of the transient pattern reversal VER was done by Halliday and Michael,[18] who found that the largest amplitude responses were recorded at electrodes located 5 to 7·5 cm in front of the inion, a site anterior to the striate cortex. They concluded that the major deflection occurring at approximately 100 ms is generated in extrastriate cortex.

Our studies demonstrate that return of inner retinal function, with no damage to optic nerve myelin, causes no alteration in VER latency. This phenomenon suggests that the inner retina responds in an all-or-none fashion. Current understanding of retinal electrophysiology supports this interpretation. With visual excitation the majority of retinal neural cells respond in a slowly graded manner, with the exception of retinal ganglion cells and some amacrine cells, where depolarisation leads to an all-or-none action potential.[21 22] With interruption and subsequent return of inner retinal activity there is a gradual and progressive return of VER amplitude, presumably reflecting the number of functioning ganglion cells. yet an immediate restitution of latency occurs, possibly due to the all-or-none action potentials of the retinal ganglion cells.

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British Journal of Ophthalmology, 1982, **66**, 386–388

Oxytetracycline in the treatment of ocular rosacea: a double-blind trial

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SUMMARY Thirty-five patients with ocular rosacea were admitted to a trial of systemic oxytetracycline, 250 mg b.d. for 6 weeks. Oxytetracycline produced a significantly higher number of remissions than the placebo, 11/35. With repeated or continuous treatment 19/35 patients achieved a sustained remission for 8 months. There were no side effects. The nonspecific signs of ocular rosacea responded well to the treatment, but no permanent change in the conjunctival or corneal vascularisation occurred.

Rosacea is a common condition affecting the skin of the face, with less frequent involvement of the eyes. Nonspecific ocular complications are similar to those found in patients with seborrhoea, blepharitis, recurrent chalazia, styes and trichiasis, hyperaemic conjunctivitis, with occasional marginal corneal infiltrates or ulcers. Specific complications include nodular conjunctivitis and episcleritis, which are rare, and the typical progressive keratitis which occurs in 5% of patients with rosacea.[1]

Oxytetracycline given orally in low dosage for more than 6 weeks is a well recognised treatment for rosacea of the skin[2–4] and is also reassuringly safe.[5–7] Tetracycline has been used topically in ocular rosacea,[8] and there is increasing evidence that rosacea keratitis may also respond to systemic tetracyclines.[1 9–11]

The purpose of this study was to assess the validity of these observations by means of a double-blind limited cross-over trial.

Material and methods

Patients attending dermatology clinics with confirmed rosacea were questioned for possible eye symptoms. Sixty-five were subsequently screened by an ophthalmologist and were admitted to the trial if their symptom and sign score (see below) reached a minimum level and if there were no general contraindications to the use of tetracyclines—pregnancy and lactation, hepatic or renal disease, drug allergy, or chronic bronchitis. Thirty-five patients were admitted to the trial.

Symptoms and signs were scored as absent (0), moderate (1), or severe (2). Symptoms were listed as: irritation, discharge, swelling of lids, redness, photophobia, pain, loss of sight. Signs were listed as: redness, swelling, discharge and chalazia for the eyelids, and redness, nodules, dilatation of vessels, tortuosity of vessels and microaneurysms for the conjunctiva and new vessels, superficial punctate keratitis, infiltrates, ulcers, and healed scars for the cornea. Left and right eyes were assessed separately. The maximum score for either eye was therefore 14 points for symptoms and 28 points for signs. A minimum of 25% score for symptoms and signs was required for admission to the trial.

On admission to the trial treatment was started with 250 mg unmarked identical capsules containing either oxytetracycline dihydrate (Clinimycin) or a placebo of identical appearance composed of dextrose. Either capsule was taken in a dose of one capsule twice daily on an empty stomach. No local eye treatment was given.

The trial was divided into treatment periods. These were defined as a 6-week period on the drug or placebo followed by a 6-week observation period on

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no drug (to allow for possible carry-over effects). Patients were kept on the trial for a minimum of 3 treatment periods. They were examined every 6 weeks.

Those who responded to the first course of treatment were left untreated but received the same agent if a relapse occurred. Those who failed to respond to the initial treatment were crossed over to the other agent for the next period of treatment. Thus any patient who failed to respond to the initial treatment always received the active drug. Those patients responding to the initial agent were not crossed over in case possible delayed response affected treatments in a relapsing case. All those involved in the clinical examination of the patients were unaware whether drug or placebo was being administered. The trial was thus double-blind with limited cross-over.

Remissions and relapses were calculated according to the change in the symptoms and signs score. A full remission required a reduction of >60% and a partial remission between 30 and 60%. A relapse required an increase of >30% on the score. A score <30% above or below the previous score was deemed to be no change.

ASSESSMENT OF RESULTS

(a) The number of remissions (partial and full) was compared statistically (χ^2 test) with the number who did not remit—for the first treatment period.

(b) The subsequent periods of treatment were not randomly allocated and therefore not subject to statistical analysis. The results are listed according to the number of remissions obtained after one, 2, or 3 courses of the drug or placebo, and whether such remissions were sustained or not after cessation of treatment.

(c) Side effects were noted.

(d) The response of the nonspecific and specific signs of ocular rosacea to treatment by oxytetracycline and placebo were noted.

Results

Details of the 35 patients admitted to the trial are listed in Table 1.

Table 1 *Details of 35 patients in oxytetracycline trial*

	No. of patients	*Time of follow-up (months)*
(1) Remission maintained after a course of drug	5	3–6
(2) Remission maintained after 2 courses of drug	7	2–5
(3) Remission maintained after 3 courses of drug	4	2–5
Sustained remissions after cessation of drug	16	
(4) Remission maintained only by treatment	3	5–8
(5) Remission maintained by placebo	4	3–12
(6) Unchanged by treatment with drug	2	
(7) Unchanged by treatment with placebo	5	
(8) Made worse by drug	2	
(9) Made worse by placebo	1	
(10) Withdrawn from trial	2	
Total patients	35	

The remissions over the first treatment period are shown in Table 2. There was a significantly higher rate of remission (partial and full) for patients taking oxytetracycline ($p<0\cdot05$).

Complications/side effects of the treatment. Two patients withdrew from the trial. One complained of nausea and sickness and refused to take any more tablets; the tablets were subsequently found to be the placebo. The other patient developed a corneal ulcer and had to be given specific topical treatment.

No other systemic or local complications were attributable to the oxytetracycline or placebo.

Response of individual signs to treatment. The nonspecific signs—lid swelling, redness, blepharitis, chalazia, and conjunctival hyperaemia responded well to treatment. Conjunctival nodules, seen in one patient, regressed during treatment. Microaneurysms developed during exposure to oxytetracycline. Corneal infiltrates, marginal ulcers, and superficial punctate erosions responded to treatment. No change was noted in new vessels of the cornea or healed scars of the cornea.

There was a delay in response to oxytetracycline of about 2 weeks in most patients. Relapses generally occurred 2-3 weeks after stopping oxytetracycline but were occasionally immediate.

Discussion

It is difficult in ocular rosacea, where spontaneous exacerbations and remissions occur, to be sure whether clinical improvement is related to specific drug treatment or is merely part of the natural

Table 2 *Remissions/nonremissions for oxytetracycline/placebo over first treatment period*

	Oxytetracycline	*Placebo*	*Total*
No. of remissions	11	5	16
No. without remission	6	13	19
Total	17	18	35

$\chi^2=4\cdot8$, $p<0\cdot05$.

variability of the disease. This trial showed a significantly greater incidence of remissions with oxytetracycline than with a placebo. Assessments were made after 6 weeks treatment with oxytetracycline 250 mg b.d. On this dosage patients who responded began to do so about 2 weeks after starting treatment. Patients who relapsed after initial improvement did so about 2 weeks after stopping oxytetracycline. Repeated courses of treatment with the same dose achieved lasting remission 3–6 months after stopping treatment. Three patients required continuous treatment to maintain remission for periods of 5–8 months.

This regimen of treatment with oxytetracycline is that used successfully by dermatologists in the treatment of rosacea of the face. In their ocular trial Jenkins *et al.*[11] found poor results with tetracycline 250 mg q.i.d. for 3 weeks followed by one week off treatment. They subsequently increased the dose to 250 mg q.i.d. for 4 weeks. Maximum remission occurred 4 days to 3 weeks after starting treatment. Thirty-six of their 37 patients improved. Fifteen obtained complete remission. Five needed to be kept on oxytetracycline. These results are similar to ours, which also confirm the results of Brown and Shahinian.[10]

The remissions were mainly due to improvement in the nonspecific signs of rosacea—blepharoconjunctivitis. Acute signs—corneal infiltrates and nodules—also improved, but there was no reduction in the vascular element of conjunctiva or cornea; indeed in one patient fresh microaneurysms appeared during a successful course of treatment.

Ocular rosacea responds to low-dosage treatment with oxytetracycline, 250 mg b.d. Remissions may be obtained after one, 2, or 3 6-week courses or may require continued therapy. There is a 2-week lag in response to initial treatment and a variable carry-over effect after stopping treatment.

Systemic oxytetracycline is thus a useful and safe treatment for ocular rosacea as well as rosacea of the face.

CONCLUSIONS

(1) Oxytetracycline in a dose of 250 mg b.d. yielded more remissions than the placebo, 11/17 (65%) over a period of 12 weeks (6 weeks on treatment, 6 weeks without treatment). (2) Oxytetracycline produced remissions in 19/35 (54%) with repeated courses or continuous treatment. (3) Oxytetracycline sustained remissions after cessation of treatment in 16/35 (45%). (4) No complications or side effects were attributable to oxytetracycline. (5) Nonspecific signs responded well to treatment by oxytetracycline. (6) No permanent change or improvement in conjunctival microaneurysms, corneal vascularisation, or scarring was seen.

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Double-masked controlled clinical trial of 5% tolmetin versus 0·5% prednisolone versus 0·9% saline in acute endogenous nongranulomatous anterior uveitis

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SUMMARY A double-masked controlled clinical trial of 5% unpreserved tolmetin versus 0·5% prednisolone versus 0·9% saline in acute endogenous nongranulomatous anterior uveitis was carried out on 100 patients. 69% of the prednisolone-treated patients were judged 'cured' at the end of the 3-week study. This is compared with a cure rate of 47% for the tolmetin-treated patients and 53% for the placebo (saline) group. No statistically significant difference was established between the 3 groups.

1-methyl-5-p-toluoylpyrrole-2-acetic acid (tolmetin) is a nonsteroidal compound with antiprostaglandin property. It has been widely used in the treatment of rheumatic disorders, and its effects are well documented.[1 2] Tolmetin has had considerable anti-inflammatory activity when used topically in experimentally induced ocular inflammation in the rabbit (D. Gilbert, Smith and Nephew Ltd, personal communication), but its effectiveness in treating ocular inflammation in man has not been assessed. This trial was therefore designed to compare the efficacy of tolmetin with that of a widely used steroidal preparation, prednisolone disodium phosphate, and a placebo, saline, in the treatment of acute endogenous nongranulomatous unilateral anterior uveitis.

Patients and methods

The trial was conducted double-masked with unpreserved tolmetin 5% prednisolone (Predsol) 0·5%, and preserved sterile saline 0·9%. One hundred patients who presented consecutively in the Casualty Department of St Paul's Eye Hospital, Liverpool, during the period September 1980 to February 1981 with unilateral acute endogenous non-granulomatous anterior uveitis were referred to one of the 3 observers.

Pregnant women, patients under the age of 16, patients with one eye, and those on systemic or topical steroids were not included.

Consent having been obtained, each patient was assigned a trial number which randomly allocated him or her to one of the 3 treatment groups. Patients were instructed to instil the trial drops every 2 hours during the waking period and also atropine 1% drops once a day. At the first visit a full clinical history was taken, and the patient's symptoms, visual acuity, degree of ptosis, signs of inflammation, and intraocular pressure were assessed. The patient's symptoms and signs were scored on a 0–3 severity scale. Further assessments were carried out on days 3, 7, 14, and 21, and the frequency of treatment was accordingly adjusted.

The trial was concluded on day 21. When possible a given patient was assessed by the same observer throughout the study.

Patients judged to be getting worse or who developed bilateral disease were taken off the trial and treated as indicated.

Results

Six patients were excluded from analysis, 5 failed to reattend, and one developed bilateral disease. Thus 32 patients were allocated to prednisolone, 32 to tolmetin, and 30 to saline. In these treatment groups 8, 10, and 12 patients respectively were judged to have failed to respond within a 15-day period and had their treatment altered. The saline-treated group had the highest percentage of patients withdrawn as treat-

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ment failures during the trial at 3, 7, and 14 days, but by the end of the trial (day 21) the tolmetin-treated group had the highest percentage of patients classified as treatment failures (Table 1).

At the conclusion of the trial 22 patients who received prednisolone, 15 who received tolmetin, and 16 who received saline were judged cured. This gives a cure rate for prednisolone of 69%, tolmetin 47%, and saline 53%. The difference between the groups is not statistically significant.

All the treatment groups showed statistically significant improvement in total symptom scores at 3, 7, 14, and 21 days (Wilcoxon signed ranks test, $p<0{\cdot}025$). The prednisolone group showed statistically significant improvement in total clinical sign scores at 3, 7, 14, and 21 days, while the tolmetin group did not show a significant reduction in total sign scores until the 14th day, and the saline group showed a significant reduction only at 21 days.

When the overall scores, that is, symptoms and sign scores, were taken together (which determined whether the patient was judged cured or failed), no statistically significant difference was detected between the groups at 3, 7, 14, and 21 days, though the prednisolone-treated group of patients had the highest percentage of patients cured at all stages in the trial (Table 2).

Table 1 *Percentage treatment failures*

Treatment	*Day 3*	*Day 7*	*Day 14*	*Day 21*
Prednisolone	9%	22%	25%	31%
Tolmetin	13%	19%	31%	53%
Saline	23%	37%	40%	47%

Table 2 *Percentage cure rate*

Treatment	*Day 7*	*Day 14*	*Day 21*
Prednisolone	6%	31%	69%
Tolmetin	3%	19%	47%
Saline	3%	20%	53%

Discussion

Prostaglandins are naturally occurring substances

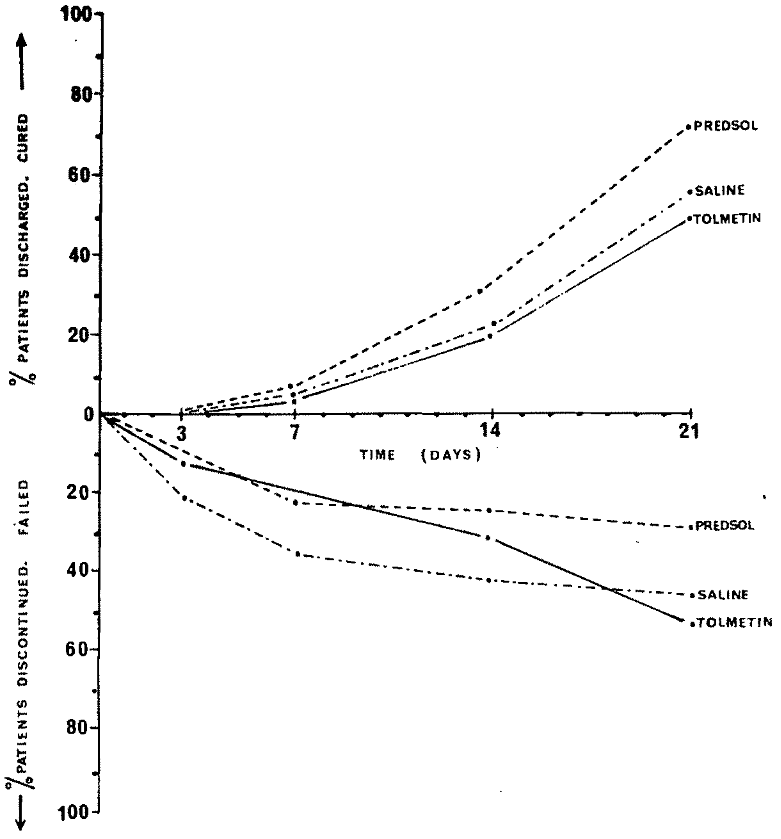

Fig. 1 *Patient progress through trial.*

which can be found in the conjunctiva and the anterior uvea.[3-6] Arachidonic acid and dihomo-y-linoleic acid are influenced by prostaglandin synthetase to form PGE and PGE_2 respectively, which appear to influence inflammation via cyclic AMP.[7] Irritation of the eye or the administration of arachidonic acid result in hyperaemia, miosis, breakdown of the blood aqueous barrier, ultrafiltration of macromolecules, and an increase in intraocular pressure. Similar effects can be seen in anterior uveitis.[7] The mode of action of nonsteroidal anti-inflammatory compounds is thought to be by the inhibition of prostaglandin synthetase. Various classes of prostaglandin inhibitors have been used in the treatment of uveitis, for example, aspirin, oxyphenbutazone, steroids.[8-12] Tolmetin is a potent inhibitor of prostaglandin synthetase, acting in a competitive reversible manner, and ranks with indomethacin in vitro in this respect.[13] Steroids are poor inhibitors of prostaglandin synthetase, and their usefulness is limited in the treatment of acute ocular inflammation by their potential side effects, namely, potentiation of viral, bacterial, and fungal infection[14-16] and an unpredicatable rise in intraocular pressure in steroid responders.[17-19]

In this series the reduction in symptom scores in all 3 groups can be attributed to atropine drops and or the spontaneous behaviour of the disease.

Clinical sign scores at day 14 of the trial showed tolmetin to be somewhat quicker than saline but took longer than prednisolone to become statistically significant. However, on completion of the trial period 47% of tolmetin-treated patients, 53% of saline-treated patients, and 69% of prednisolone-treated patients were judged to be cured (Fig. 1). No statistically significant difference could be determined between the 3 groups.

Thus the efficacy of tolmetin and steroids in treating nongranulomatous anterior uveitis in man does not appear to be similar to that reported when it was used in the treatment of experimentally induced uveitis in rabbits (D. Gilbert, personal communication).

The fact that 50% of the placebo-treated patients were deemed cured at 21 days is further evidence that nongranulomatous anterior uveitis is a self-limiting disease.[20] Unfortunately it is not at present possible to predict which cases will terminate spontaneously, so all must be treated initially.

We thank Smith and Nephew Ltd for providing the tolmetin (McNeil Pharmaceuticals), and D. Gilbert, and K. M. Shawley, both of Smith and Nephew Research Ltd, for their personal assistance.

We are grateful to Mr R. Mapstone for his advice and also to the other consultants at St Paul's Eye Hospital who allowed us to include their patients in this trial. Our thanks to G. Scarisbrick for her secretarial help.

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British Journal of Ophthalmology, 1982, **66**, 392–395

Severe exophthalmos secondary to orbital myopathy not due to Graves's disease

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SUMMARY An 18-month-old white female child presented with severe bilateral exophthalmos. She was thought to have Graves's disease because her orbital CT scan showed massively enlarged extraocular muscles. She was subsequently found to have myelomonocytic leukaemia. This was treated with radiation, with rapid resolution of her exophthalmos and exposure keratitis.

Pathologically enlarged extraocular muscles are most commonly found in patients with Graves's disease, for which this is virtually pathognomonic. B-scan ultrasonography has been the best means of making the diagnosis of enlarged extraocular muscles until recently, when high-resolution orbital computerised axial tomographic (CT) scanning has been used to verify their enlargement. We recently treated a young child with bilateral proptosis presumed secondary to Graves's disease. Both B-scan ultrasonography and an orbital CT scan revealed multiple enlarged extraocular muscles consistent with the diagnosis of Graves's disease. On further investigation she was found to have an acute leukaemia. The finding by orbital CT scan of enlarged extraocular muscles in acute leukaemia is unique and forms the basis of the following case report.

Case report

This 18-month-old white female developed bilateral conjunctival hyperaemia on 5 November 1980 and was initially treated by the referring physician with topical and oral antibiotics for presumed conjunctivitis. The redness continued, and bilateral proptosis developed. She was admitted to his hospital on 19 December 1980 for examination. A CT scan showed bilateral soft tissue thickening with involvement of both superior and lateral rectus muscles. The examination included skeletal x-rays, analysis of blood and urine electrolytes, proteins, and enzymes by Sequential Multiplying Analyzing Computer, and blood cultures. Thyroid functions, including L-thyroxine (T4), tri-iodiothyronine (T3), free thyroxine index (FTI), and thyrotropin (TSH) were normal. A trial of intravenous antibiotics and systemic steroids was unsuccessful. The proptosis increased and she was unable to close her lids over her eyes (Fig. 1).

She was then referred to the Shands Teaching Hospital for possible decompressive surgery. At the time of admission she was on prednisone, 10 mg by mouth twice a day (maximal dose for body weight) for 5 days. She was unable to fix or follow OU. There was marked proptosis, greater on the right than left side (Hertel measurements were 29/27 mm) (Fig. 1). Firm tissue was noted between the lids and minimal retropulsion. Motility was markedly decreased in all directions. Pupils were 4 mm OU with 4+ light reaction and no evidence of Marcus Gunn pupil. External examination revealed an epithelial defect of OD with clear corneas and no infiltrates. Fundus

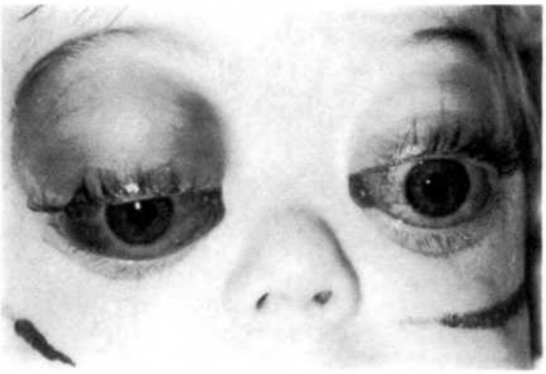

Fig. 1 *Patient on admission (Hertel exophthalmometer readings of 29 and 27 mm).*

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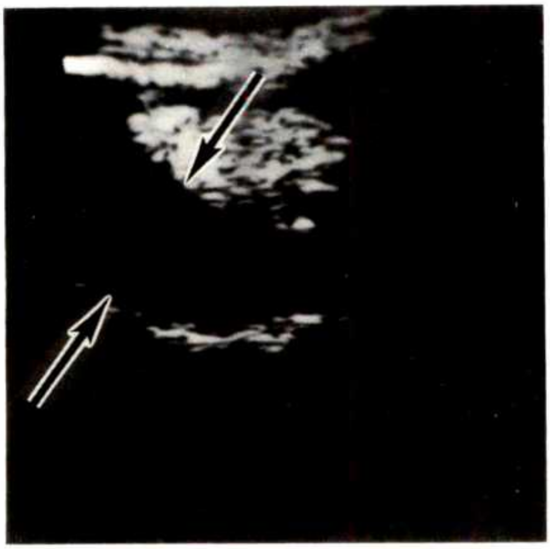

Fig. 2 *B-scan echography demonstrating marked enlargement of extraocular muscle (horizontal section of left orbit; arrows indicate markedly increased thickness of lateral rectus muscle).*

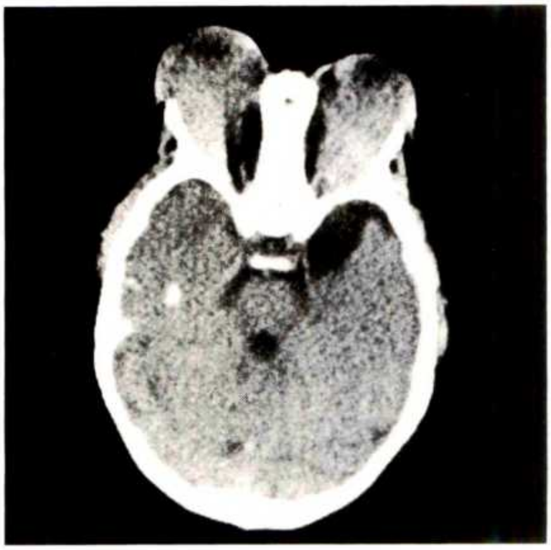

Fig. 4 *CT scan showing marked and symmetrical enlargement of superior rectus muscles.*

examination showed normal disc and vessels OU. B-scan echography showed enlarged extraocular muscles (Fig. 2). The rest of the examination was normal except for a left peripheral seventh nerve palsy.

The patient was begun on ocular lubricants every 1 hour OU. The next morning a CT scan (Figs. 3, 4) showed massive enlargement of superior and lateral recti, bilaterally, with no evidence of a retro-orbital mass. A T3 radioimmunoassay was normal, and tests for thyroid antibody, thyroidal globulin antibody, and microsomal antibodies were negative. The haemoglobin was 11·5 g/dl and the leucocytes were $4{\cdot}8\times10^9$/l, with 98% lymphocytes. A microscopic examination showed smudge cells and atypical lymphocytes more than 50%. A bone marrow biopsy was performed (Figs. 5, 6), and a diagnosis of acute myelomonocytic leukaemia was made.

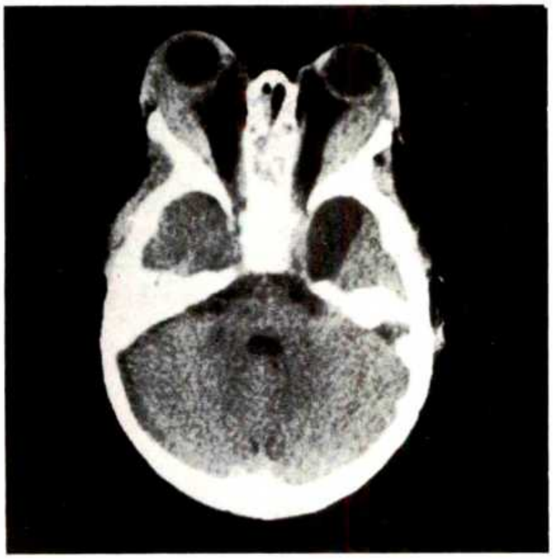

Fig. 3 *CT scan showing marked and symmetrical enlargement of lateral rectus muscles.*

The patient had whole brain and orbit irradiation, and within 48 hours a marked decrease in proptosis was noted. By the fifth day she could close both her eyes with a marked decrease in proptosis (shown in Fig. 7). The patient was begun on systemic chemotherapy, consisting of vincristine and cyclophosphamide. She was doing well at the time of discharge.

Discussion

Orbital involvement may be the presenting sign in acute leukaemia.[1] In our case the diagnosis of leukaemia was obscured by CT scans demonstrating multiple enlarged extraocular muscles. This finding was most consistent with dysthyroid ophthalmopathy. Graves's disease occurs not infrequently in children comparable in age to our case, with a propensity to

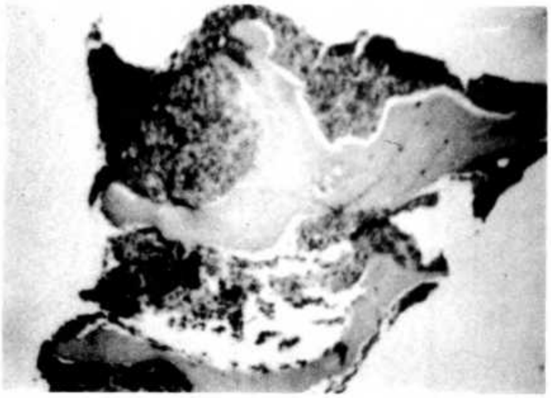

Fig. 5 *Bone marrow showing marked cellularity. (Haematoxylin and eosin, ×0·6).*

affect females.[2,3] 95% of young patients with dysthyroid ophthalmopathy in one recent series had proptosis.[2] Frequently patients with endocrine exophthalmos have normal thyroid function tests and no circulating antithyroid antibodies.[4] And 'Graves' ophthalmology is the most common cause of proptosis in children. . . .'[2]

Other disease processes considered in the differential diagnosis included neuroblastoma, which may present initially with bilateral proptosis[5] and enlarged extraocular muscles on CT scan.[6] However, there was no abdominal mass. Other less likely causes, such as bilateral orbital cellulitis and cavernous sinus thrombosis, were ruled out owing to lack of toxic manifestations or foci of infection in our patient. Pseudotumor was thought unlikely because of its usual unilateral presentation and our patient's unresponsiveness of high dose steroids.

In acute lymphoblastic/lymphocytic leukaemia diffuse conjunctival and orbital infiltrations have been reported.[7,8] Reticulum cell sarcoma caused bilateral orbital masses in several cases with acute monocytic leukaemia.[9,10] Acute myelocytic leukaemia is associated with a peculiar greenish tumour called chloroma that has caused bilateral orbital masses and exophthalmos.[9,11] All the aforementioned cases were reported before the CT scan era, and thus it is not known if they also had involvement and enlargement of the extraocular muscles. Histopathological study of orbital tissue obtained at biopsy in these cases did not, however, show involvement of the extraocular muscles. In our case biopsy was considered but obviated when the diagnosis of leukaemia was made.

Further histochemical studies confirmed that our child was afflicted with myelomonocytic (previously designated monocytic) leukaemia. There is a relationship between reticulum cell sarcoma and monocytic leukaemia. However, only a few cases of reticulum cell sarcoma have been reported to occur in patients with acute myelomonocytic leukaemia.[9,10] Most cases of reticulum cell sarcoma occur as a systemic disease.[12] It is most unlikely that our patient has this association. All evidence suggests that the orbital deposits causing the proptosis in our case are due to leukaemic cell infiltration in the extraocular muscles. Straatsma and Allen[13] have shown histopathologically that extraocular muscles can be

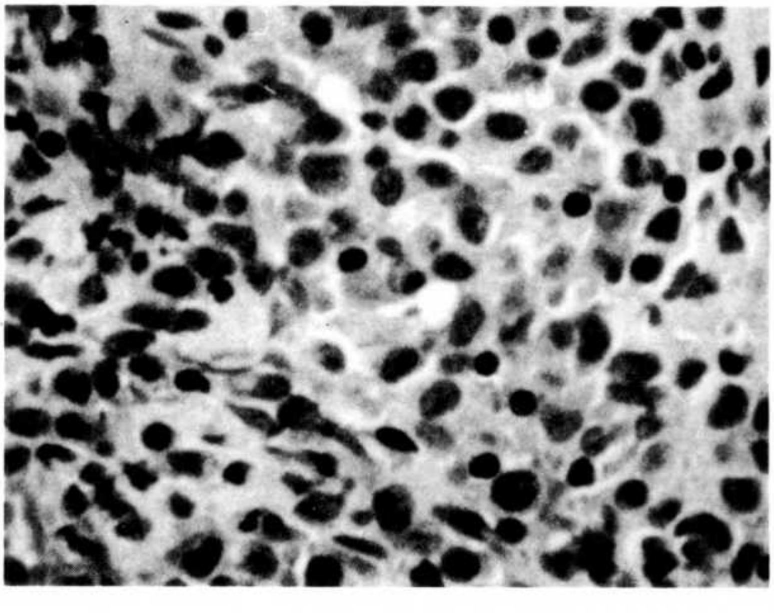

Fig. 6 *Bone marrow showing monocytic myeloblasts. (Haematoxylin and eosin, ×450).*

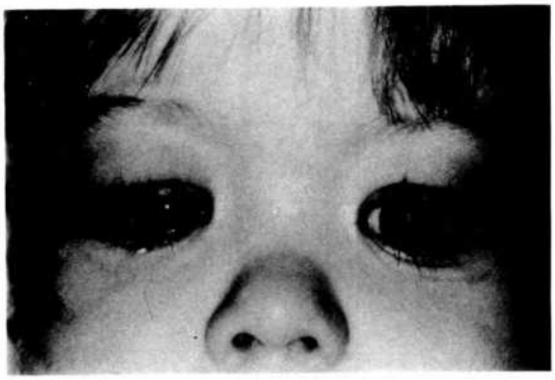

Fig. 7 *Patient after 5 days of radiotherapy.*

infiltrated by leukaemic cells, as presumed in our case.

Enlarged extraocular muscles, especially when multiple and bilaterally symmetrically affected, are nearly always due to Graves's exophthalmopathy.[14] Although the most commonly affected muscles in Graves's disease are the inferior and medial rectus muscles, isolated involvement of the lateral and superior rectus muscles has been reported.[6 14] Other associated diseases with enlarged extraocular muscles by CT scan are pseudotumour, which affected only one muscle in all 7 cases reported; carotid cavernous fistula, with the distinguishing feature of enlarged superior ophthalmic vein in addition to the enlarged muscles; and various malignancies, none of which was a leukaemia.[6]

Neoplasms associated with enlarged extraocular muscles on CT scan cause the enlargement by direct infiltration or compression of the muscle with venous congestion.[6] In these reported cases[6] a separate mass causing muscle compression or infiltration could be verified by CT scan, as opposed to our case in which a separate mass was not associated with enlarged extraocular muscles.

This research was supported in part by an unrestricted departmental grant from Research to Prevent Blindness Inc.

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British Journal of Ophthalmology, 1982, **66**, 396–397

Orbital tuberculosis in childhood

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SUMMARY An 11-year-old Indian girl living in England developed proptosis due to tuberculosis of the orbit. The proptosis regressed and she recovered fully after chemotherapy. While malignancy, developmental anomalies, and nontuberculous infections are commoner causes, a tuberculin test should be included among the investigations of children with proptosis.

Orbital tuberculosis is extremely rare,[1] especially in childhood and particularly in the Western Hemisphere. We report here on an 11-year-old girl who presented with proptosis due to tuberculosis.

Case report

An 11-year-old Indian girl was admitted in May 1978 to Birmingham Children's Hospital for investigation of proptosis. She complained of intermittent headache for 2 months and of protuberance of her left eye, fever, and a painful swelling above her left knee for 2 weeks. Three years previously both of her parents had been treated for tuberculosis, but she had not been given BCG immunisation.

On examination she was pyrexial and pale, with a soft-tissue swelling over the lower lateral aspect of the left femur and proptosis upwards and outwards of the left eye.

Investigations included Hb 10·4 g/dl, leucocytes $6 \cdot 7 \times 10^9$/l, and erythrocyte sedimentation rate (ESR) 74 mm/h. A chest *x*-ray showed a paratracheal lobular mass without hilar involvement. Skeletal *x*-rays showed a destructive metaphyseal lesion on the lateral aspect of the lower femoral shaft, with scalloped internal margin, periosteal reaction, and associated soft-tissue swelling, and also a soft-tissue mass on the inferior margin of the left orbit. A CT scan (Fig. 1) showed a soft-tissue mass in the left orbit on the posterolateral and retrobulbar aspects, pushing the globe forward. The posterolateral wall was thinned, but no major destructive lesion was seen. Bone marrow aspirate was normal. Her Mantoux test, 1:10000, was strongly positive. Biopsy of the femoral lesion showed tuberculosis, and *Mycobacterium tuberculosis* was cultured from this and early morning urine specimens.

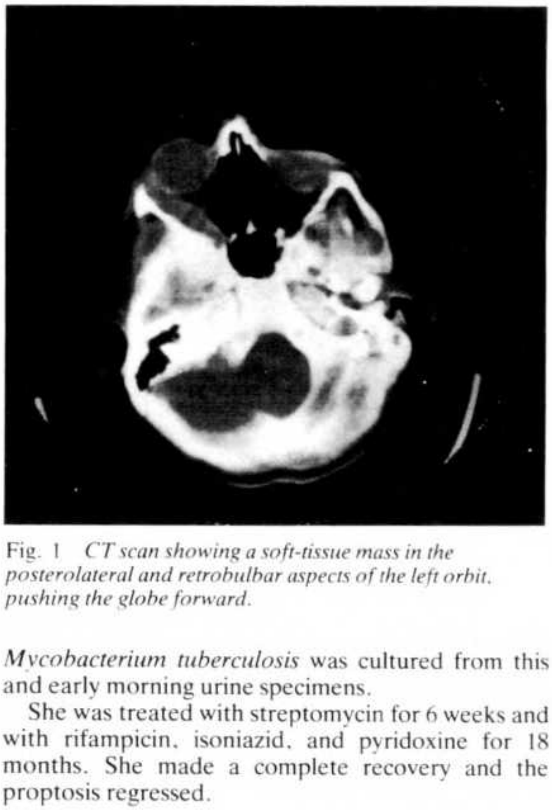

Fig. 1 *CT scan showing a soft-tissue mass in the posterolateral and retrobulbar aspects of the left orbit, pushing the globe forward.*

She was treated with streptomycin for 6 weeks and with rifampicin, isoniazid, and pyridoxine for 18 months. She made a complete recovery and the proptosis regressed.

Discussion

Very few patients with orbital tuberculosis have been reported in recent years. Mortada[2] described 3 from Egypt and Agrawal *et al.*[3] 14 from India, but only one case has been recorded for the past 40 years in the West, a 15-year-old Negro with an orbital mass and

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pulmonary tuberculosis who was diagnosed in Philadelphia after surgical exploration of the orbit.[4] The CT scan of the American boy's orbit showed appearances similar to our patient's.

Haematogenous spread from a primary tubercular focus may affect the bones of the orbit, or, as in the 3 patients described by Mortada,[2] it may lead to infection in the lacrimal ducts or glands. All ages may be affected. Orbital infection does not necessarily lead to proptosis but may also present with sinus formation, keratitis, and ectropion. The course of the disease is typically slow, and the duration of symptoms in the series studied by Agrawal *et al.*[3] ranged from 2 months to 7 years. At presentation there is nearly always evidence of widespread tuberculosis, and the tuberculin tests were positive in all the 12 patients who were reported to have been tested.[2–4]

Although malignancy, developmental anomalies, and nontuberculous infections are much commoner causes of proptosis in childhood,[5] a tuberculin test should be included among the investigations performed, as orbital tuberculosis has probably been underdiagnosed. Agrawal *et al.*[3] found 14 examples in India during 5 years.

We are grateful to the Leukaemia Research Fund for financial support, to Dr A. H. Cameron for the histopathology, and Dr R. H. George for the microbiology.

This patient was included in a series of children with unilateral proptosis reported elsewhere.[5]

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British Journal of Ophthalmology, 1982, **66**, 398–404

Stimulus and response AC/A ratios in intermittent exotropia of the divergence-excess type

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SUMMARY Objective infrared recording devices were used to measure simultaneously and continuously both accommodation and accommodative vergence to near stimuli in 4 subjects with intermittent exotropia of the divergence-excess type (2 simulated and 2 true). In addition standard clinically determined stimulus accommodative convergence to accommodation (AC/A) ratios were measured. Results showed the mean group response AC/A ratio to be 5·9/1 (range 4·5–8·0/1) with no differences between true and simulated divergence-excess. Similar AC/A ratios were found after 45 minutes of monocular occlusion. Our results clearly demonstrate relatively normal response AC/A ratios in these subjects. Thus, contrary to what is believed by many clinicians, the reduced ocular deviation at near compared with distance vision cannot be attributed primarily to an abnormally high AC/A ratio. We believe that fusional convergence after-effects and/or proximal convergence effects contribute to inflate the clinically determined stimulus AC/A ratios.

The divergence excess type of intermittent exotrope, with the deviation being greater at distance than at near vision,[1] is commonly believed to have a very high accommodative convergence to accommodation (AC/A) ratio.[2–5] This notion has been based largely on distance/near measurements of the horizontal oculomotor exodeviation (i.e., tropia or phoria). The average deviation is 29 Δ at far and 9 Δ at near,[6] resulting in an average stimulus AC/A ratio of approximately 14·0/1. However, reported values of the AC/A ratios in these patients show much variation. Ogle *et al.*[7] found the mean stimulus AC/A ratio to be 3·0/1 using the fixation disparity method.[8] Moore *et al.*,[9] grouping all exotropes (divergence excess, convergence insufficiency, and basic exotropes) together (45% were the divergence excess type), found the mean stimulus gradient AC/A ratio to be 4·7/1. Calculations from Brown[5] suggest presence of a stimulus AC/A ratio of 13·0/1 or greater based on the +3·00 dioptre gradient technique. Von Noorden[10] found a wide range of stimulus AC/A ratios (3·3 to 9·0) using the ±3·00 dioptre gradient technique in a large sample of patients. In 2 cases presented by Burian and Smith[11] gradient stimulus AC/A ratios were 6·0/1 and 8·0/1, while they were 14·0/1 by the distance/near phoria method.

There are 2 basic problems with the above mentioned studies. First, only stimulus AC/A ratios were determined. One is never certain of the actual accommodative response but rather assumes it to be equal to the stimulus demand. This assumption results in an 8% underestimation of the AC/A ratio in normal persons,[12] but the correction factor is unknown in patients with binocular vision abnormalities. Secondly, the distance/near type measures of the oculomotor deviation are probably contaminated, that is, inflated by proximal convergence effects,[13 14] which may be more dramatic in intermittent exotropes than in normal persons.[7] Thus, we sought to determine and compare stimulus and response AC/A ratios under several test conditions in 4 patients with the divergence excess type of intermittent exotropia. The AC/A ratio in these patients has important clinical implications, especially with respect to determination of appropriate surgical procedures to attain binocular alignment,[15] as well as in understanding the contribution of the components of vergence in Maddox's sense.[16]

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Patients and methods

All subjects had intermittent exotropia at distance (6 m) and an exotropia/phoria at near at least 10 prism dioptres less than at distance when fixating a 20/25 Snellen letter, and thus were classified as divergence excess.[17] Visual acuity was at least 20/20 in each eye. Stereopsis was at least 40 seconds of arc as determined on the Randot test.[18] Only adult subjects (aged 20-26 years, 3 females and 1 male) were tested, as rigorous test conditions essential to obtain objective measurements necessitated the use of a bite bar, head rest, and chin rest to stabilise the head for extended periods of time. Owing to the rigour of our test conditions objective recordings from 2 other subjects were discarded because of baseline shifts and gain changes in the records resulting from the inability to remain very still in the apparatus. Corrective lenses were worn during all testing.

Stimulus AC/A ratios were determined by 4 clinical methods.[19] (1) distance/near cover test: the alternate cover test was performed while the subject fixated and maintained in clear focus a 20/25 Snellen letter at 6 m and a J1 print at 40 cm. Prisms were used to neutralise the angle of deviation. Both subjective and objective angles of deviation were measured. (2) Gradient test at near: the subject fixated and maintained in clear focus a J1 print at 40 cm, while the horizontal deviation was neutralised both objectively and subjectively with prisms. Lenses of the following powers, +2·00, +1·00, plano, −1·00, and −2·00 dioptres were placed before both eyes and were used to calculate the AC/A ratio: (3) gradient test in a synoptophore: the subject viewed a superpositioned target which subtended an angle of 1 degree. Lenses of the following powers, plano, −1·00, −2·00, and −3·00 dioptres were placed before both eyes and were used to calculate the AC/A ratio based on subjective and objective neutralisation of the deviation. (4) Phorometric method: phorias, if possible, were measured in a phoropter with vertical dissociation to induce diplopia at distances of 6 m and 40 cm. The subject fixated and maintained in clear focus a 20/25 Snellen letter at 6 m and a J1 print at 40 cm. The AC/A ratio was calculated by comparing distance and near alignment values as related to the change in fixation distance.

On completion of the initial clinical portion the objective response and stimulus AC/A ratios were measured. An infrared optometer (Fig. 1) was used to monitor dynamic changes of accommodation in the fixating left eye. The optometer had a band width of 5 Hz, a resolution of 0·12 dioptres, and linearity of −6 to +6 dioptres. This dynamic optometer has been fully described elsewhere.[20] The accommodative stimulus was a fine-lined cross etched on the front surface of a clear piece of Plexiglass. The crosses subtended an angle of 1·5 or 3·0 degrees at distance and near respectively. The fine lines forming the crosses subtended an angle of approximately 2-4 min arc. The experimenter used a silent 2-position switch to illuminate either the far (67 cm, 1·5 D) or near (33 cm, 3·0 D) stimulus with temporal randomisation of the step inputs. All testing was done in a dark room, only the cross target being allowed to act as the primary stimulus to accommodation. An infrared scleral-reflection eye movement system[21] was used to monitor dynamic changes of accommodative vergence in the occluded right eye. The eye movement system had a band width of 40 Hz, a resolution of 0·5 degrees, and linearity of ±10 degrees (with DC bias to compensate for the outward deviation of the occluded, verging eye). The eye monitoring system was placed 10 mm from the eye. Calibration and cross-talk checks were performed before and after each test session. The accommodation response, accommodative vergence response, and stimulus were recorded simultaneously on a strip chart recorder (band width 150 Hz), from which the response AC/A ratios were calculated. Following the initial transient component in response to a stimulus change, the steady-state response was estimated by eye for the subsequent 2–5-second part of the record.

All stimulus and response AC/A ratios were repeated after 45 minutes of monocular occlusion to

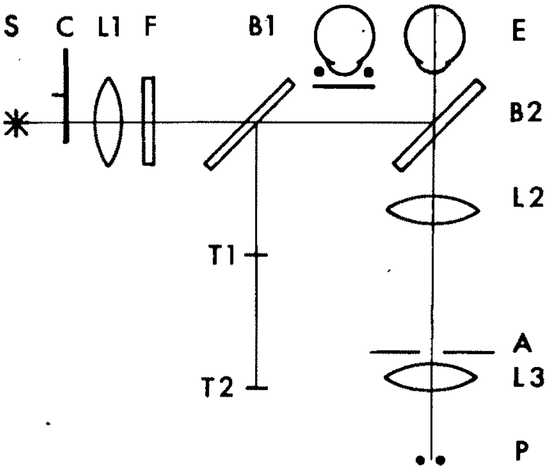

Fig. 1 *Top view of apparatus used to measure accommodation and accommodative vergence consisting of 4 components: (1) Light source (S=halogen lamp, C=light chopper, L1=collimating lens, F=infrared filter, B1 and B2= beam splitters, and E=eyes. (2) Targets (T2=far target, T1=near target, plus B1 and B2. (3) Accommodation monitor (P=photodetectors, A=aperture, L2 and L3=focusing lenses, plus B2. (4) Eye movement monitor (occluder, infrared emitter/detectors in front of right eye).*

Table 1 *Clinical and experimental data of subjects*

	Subject	*Cover test*[c]		*Cover test*	*Phor. D/N*	*Near gradient*	*Synopto-phore*	*Objective AC/A*				
		D	*N*	*AC/A*[d]	*AC/A*	*AC/A*	*AC/A*	$\bar{x}$[e]	*SD*	*n*	$\bar{x}$[f]	*SD*
(a)	Preocclusion											
	1[a]	12 X(T)	0	10·8/1	18·0/1	2·8/1	8·1/1	6·2/1	1·6	32	4·4/1	0·8
	2[a]	10 X(T)	0	10·0/1	8·5/1	2·5/1	7·5/1	4·9/1	1·1	23	3·6/1	0·8
	3[b]	17 X(T)	7 X	10·0/1	9·9/1	7·0/1	8·3/1	8·0/1	2·3	24	4·9/1	1·4
	4[b]	16 X(T)	4 X	10·8/1	12·7/1	7·5/1	8·6/1	4·5/1	1·1	47	3·9/1	0·8
$\bar{x}$=		13·8	2·8	10·4/1	12·3/1	5·0/1	8·1/1	5·9/1			4·2/1	
(b)	Postocclusion											
	1	20 X(T)	4 X	12·5/1	Supp.	2·8/1	4·7/1	6·4/1	1·6	18	2·9/1	0·7
	2	16 X(T)	6 X	10·0/1	8·0/1	2·5/1	5·0/1	4·5/1	0·6	10	3·7/1	0·7
	3	18 X(T)	18 X(T)	6·0/1	3·3/1	6·4/1	9·0/1	10·3/1	2·3	7	7·3/1	1·6
	4	16 X(T)	24 X(T)	2·8/1	7·3/1	6·1/1	7·0/1	4·7/1	1·6	17	4·4/1	1·4
$\bar{x}$=		17·5	13·0	7·8/1	6·2/1	4·5/1	6·4/1	6·5/1			4·6/1	

[a] True divergence excess. [b] Simulated divergence excess. [c] Unit is prism dioptres. [d] Unit for all AC/A measures is prism dioptres per dioptre. [e] Objective response AC/A ratio. [f] Objective stimulus AC/A ratio.
D = distance. N = near. Phor. = phorometric.

determine the extent of postocclusion changes, especially with respect to classification of true or simulated divergence excess.[15] Subjects were not permitted binocular stimulation between or during this second set of measurements.

Results

The results are summarised in Table 1. Abnormally high mean stimulus AC/A ratios were found with the distance/near cover (10·4/1) and phorometric (12·3/1) tests. However, with near gradient measures the mean AC/A values were clearly reduced (5·0/1, 8·1/1). Further, based on the objective findings, in which distance/near effects were minimised, response AC/A ratios were generally within normal limits (mean=5·9/1; range=4·5/1 to 8·0/1), although biased toward the high side. However, our objectively determined mean stimulus AC/A ratios were clearly within normal limits (mean=4·2/1, range=3·6/1 to 4·9/1). The most consistent pre- and postocclusion AC/A ratios were obtained with the objective technique. Pre- and postocclusion response AC/A ratios were similar in all 4 subjects, with the mean preocclusion value being within one standard deviation of the mean postocclusion value. On the basis of similarity of distance/near values of the strabismic deviation following occlusion, subjects 3 and 4 were classified as simulated divergence excess. On the basis of consistent dissimilarity of the distance/near value of the strabismic deviation following occlusion, subjects 1 and 2 were classified as true divergence excess.

The responses of 2 subjects representing each diagnostic group are presented in Fig. 2. These records provide an indication of the slight fluctuations of accommodation and of the synkinetically linked accommodative vergence during attempted steady fixation and focus on the target from which objective response and stimulus AC/A ratios were determined. Dynamic overshoots of accommodation were frequently present in the responses of subject 4, but these transients were not included in estimating the steady-state accommodation level.

Discussion

It is generally believed that the AC/A ratio is abnormally high in individuals having intermittent exotropia of the divergence excess type. Like others we too found abnormally high stimulus AC/A ratios in our subjects, but only if distance/near measurements were used in the calculation. If the near gradient or the objective technique was used, AC/A ratios were generally within normal limits, in agreement with von Noorden.[10] Further, Cooper[22] has questioned the validity of these high AC/A ratio measures, since presence of an abnormally high AC/A ratio cannot explain the following clinical findings associated with divergence excess. First, over 75% of all patients with divergence excess exhibit a dramatic increase in the near deviation following a short period of monocular occlusion.[10] Such an increase in the near deviation results in a dramatic decrease in the calculated stimulus AC/A ratio, and this is evident in our subjects 3 and 4 (Table 1). This change in the stimulus AC/A ratio is surprising, since occlusion does not affect the stimulus to accommodation. Secondly, there is frequently (25% of the cases) a

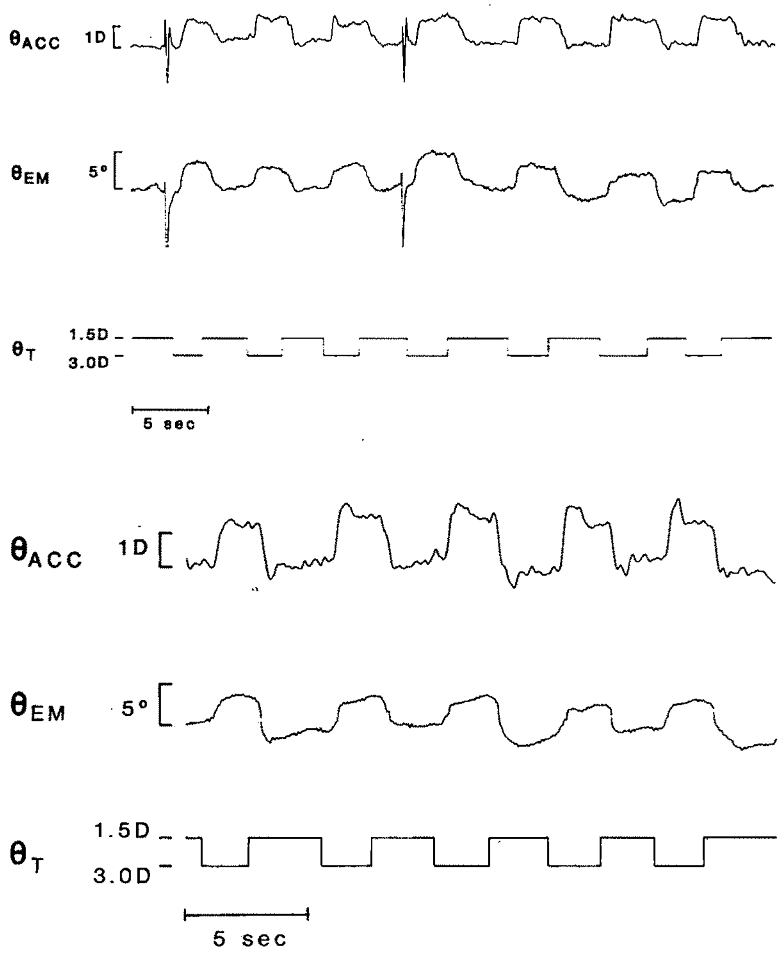

Fig. 2 *Records of accommodation in the viewing left eye (θ_{ACC}), accommodative vergence in the occluded right eye (θ_{EM}), and target position (θ_T). (a) Subject 1. True divergence excess exotropia. Two large deflections are due to blinking. (b) Subject 4. Simulated divergence excess exotropia. Dynamic overshoots of accommodation present in most responses.*

dramatic increase (4 to 10 Δ) in the distance exodeviation when the fixation distance is changed from 20 to 100 feet (6–30 m)[11] (a 0·13 dioptre change in stimulus to accommodation). Such an AC/A-related change in the exodeviation necessitates the presence of an exceedingly high (up to 100/1) AC/A ratio, which is conceptually difficult to accept. Further, it suggests gross nonlinearity of the AC/A ratio in these patients. Thirdly, a patient with an abnormally high AC/A ratio and a large exodeviation should stress his (normal) negative relative accommodation capability during periods of fusion, resulting in a complaint of intermittent blur. However, this is not commonly reported. Lastly, if the deviation is AC/A-dependent, then after surgical correction of the exotropia a large residual esodeviation should be evident at near vision. However, after operation large esodeviations rarely occur at near vision,[23] and the exotropia often recurs.[24] None of the above ideas are consistent with the notion of an abnormally high AC/A ratio in patients with divergence excess.

Others have argued in favour of the distance/near type of stimulus AC/A ratio in divergence excess patients on the basis of its clinical usefulness, especially with respect to determination of the appropriate surgical procedure for strabismus.[2–3] We do not deny, nor wish to detract from, its usefulness to the clinician. However, we believe it is important from a scientific point of view to determine the true AC/A ratio with the hope that this information will provide insight into the physiological mechanisms underlying the divergence excess condition. Our objective findings indicated relatively normal AC/A ratios. Thus the lack of a large exodeviation at near vision and the enhanced binocularity at near cannot be accounted for by evoking the use of an abnormally high AC/A ratio to align the eyes for proper binocular sensory integration. A further point supporting the objective determination of AC/A ratios in these subjects can be made with respect to the uncertainty of the clinical measures due to the presence of sensory abnormalities and also to assumptions related to the response of accommodation. Most clinical estimates of the stimulus AC/A ratio depend upon a subjective measure of vergence changes, which demands the presence of normal retinal correspondence and absence of suppression during measurements. Neither condition is always present in these patients.[25] Further, the assumption is made that the accommodative stimulus and response are equivalent, which is not true in normal persons[12] and was not the case in our patients having intermittent exotropia. Our objective recording procedure was not influenced by abnormal direction sense, as found in anomalous retinal correspondence, nor by the suppression of input to the deviated eye, as is frequently found in these patients.[25] Further, the accommodative responses were objectively recorded, which by-passed the need to make assumptions regarding the accommodative stimulus/response relationship.

While some may argue that our population of subjects with divergence excess was atypical, since their mean distance deviation (13·8 ΔXT) was less than commonly reported (29 ΔXT),[6] we believe this not to be the case. First, all subjects met the Burian-Spivey criterion[17] of having at least a 10 Δ preocclusion difference between the distance and near deviation. Secondly, as pointed out by Burian,[26] in many patients with simulated divergence excess the near deviation increases as adulthood approaches, and they begin to look like a basic exotrope with distance and near exodeviations being similar. Because of the stringent requirements essential for obtaining accurate measures of accommodation and accommodative vergence with our objective recording devices, only co-operative adults could be used, and thus our subject pool was biased in this more basic exotropic direction. Thirdly, all subjects had sensorimotor characteristics typical of the patients with divergence excess.[6] For example, there was increased frequency of exodeviation with inattention, exophoria at near vision, anomalous retinal correspondence and/or suppression while deviating, and presence of normal stereopsis when bifixating. On the basis of these arguments we believe our sample of subjects to be representative of the adult divergence excess population.

We believe that the abnormally high, clinically determined stimulus AC/A ratios are contaminated by at least 2 factors: fusional convergence after-effects and proximal convergence effects. The fusional convergence after-effect[27] refers to a transient (20 seconds or more[28]) change (up to 10 Δ) in the fusion-free position of the eyes following a short period (several seconds to a few minutes) of sustained vergence. Fusional convergence after-effects are commonly observed in normal patients as a change in the phoria position following a determination of relative vergence ranges.[27] A relative increase in esophoria is found following brief binocular fusion through base-out prisms, and a relative increase in exophoria is found following brief binocular fusion through base-in prisms.[19] Thus, in individuals having simulated divergence excess, in which there is a large relative increase in exodeviation after 45 minutes of monocular occlusion, we believe this postocclusion change is a direct manifestation of a fusional convergence after-effect resulting from sustained fusional convergence required to bring the eyes from a divergent position to one of binocular alignment on the object of interest. If the initial cover test is performed, a certain fusion-free position of the eyes is found. However, after 45 minutes of occlusion, which is apparently sufficient for decay of the fusional convergence after-effect in these individuals, a marked increase in exodeviation was revealed. This after-effect appears to be especially pronounced at near vision, where the increased frequency of fusion demand may result from increased presence and value of stimulus parameters related to fusion and processing of depth information, such as small, angular disparities, increased size of fusion contours of objects of interest within the central field, and the association of tactile information with visual information at close distances.

Any decrease in the frequency of fusion in individuals with divergence excess results in an increase in the exodeviation. This may be noted by observing the effects of fixation disparity measurements, cover test findings, and prolonged occlusion on the magnitude of the deviation. When true (full-field) dissociation does not occur, as during the measurement of fixation disparity, these patients exhibit eso- or minimal exofixation disparity.[29] The initial findings of the rapid cover test reveal an exodeviation. Prolonged occlusion results in uncovering the full extent of the exodeviation. Thus, the more complete and the longer the monocular occlusion, the greater the exodeviation. This is consistent with the notion of a decay in the fusional convergence after-effect.

The role of the fusional convergence after-effect is further supported by the results of orthoptic treatment in these patients. There is frequently a dramatic decrease in frequency and magnitude of deviation, as measured by the routine cover test, after successful orthoptic treatment.[30 31] However, prolonged occlusion will reveal the original deviation. Thus monocular occlusion appears to influence the fusional vergence system only, without affecting accommodative, tonic, or proximal vergence factors. The fact that proximal factors probably do not play a role in simulated divergence excess is evidenced by the similarly high AC/A ratios obtained with distance/near as well as gradient-type measures.

Individuals with the true divergence excess also showed abnormally high stimulus AC/A ratios by distance/near measure. However, since the *difference* in exodeviation was not affected by prolonged occlusion, a fusional convergence after-effect at near only, as was speculated in the case of simulated divergence excess, cannot explain this finding. We suggest rather that proximal convergence factors predominate, as near gradient stimulus AC/A ratios were typically much reduced relative to the distance/near values. However, we do believe that fusional convergence after-effects are also involved, but affect the vergence system at all distances approximately equally, as shown by the increase in exodeviation of the fusion-free position of the eyes at both distance *and* near. This difference in influence of a fusional convergence after-effect may be related to differences in frequency of fusion at distance and near vision in the simulated and true divergence excess patients. This idea warrants further careful investigation.

The results of our investigation lead one back to Maddox,[16] who defined the 4 components of vergence: tonic, proximal, accommodative, and fusional. He believed that accommodative vergence was primary, with fusional vergence serving only a supplementary role. Proponents of the abnormally high (stimulus) AC/A ratio in patients with divergence excess likewise suggest that accommodative vergence is the primary, and perhaps the sole, component used to align the eyes from the distance unfused (deviated) position to the near fused position. However, our finding of relatively normal (response) AC/A ratios in these patients forces one to accept a less dominant role for accommodative vergence. More recent investigations in normal persons[32 33] provide strong evidence that fusional rather than accommodative vergence is the dominant component. On the basis of our findings in individuals with divergence excess we would like to extend this concept and suggest that fusional as well as proximal vergence play important roles in the near fusion response. However, the exact proportion of each vergence component used to achieve fusion awaits further investigation.

This work was supported in part by NIH grant EY03541 to K.J.C.

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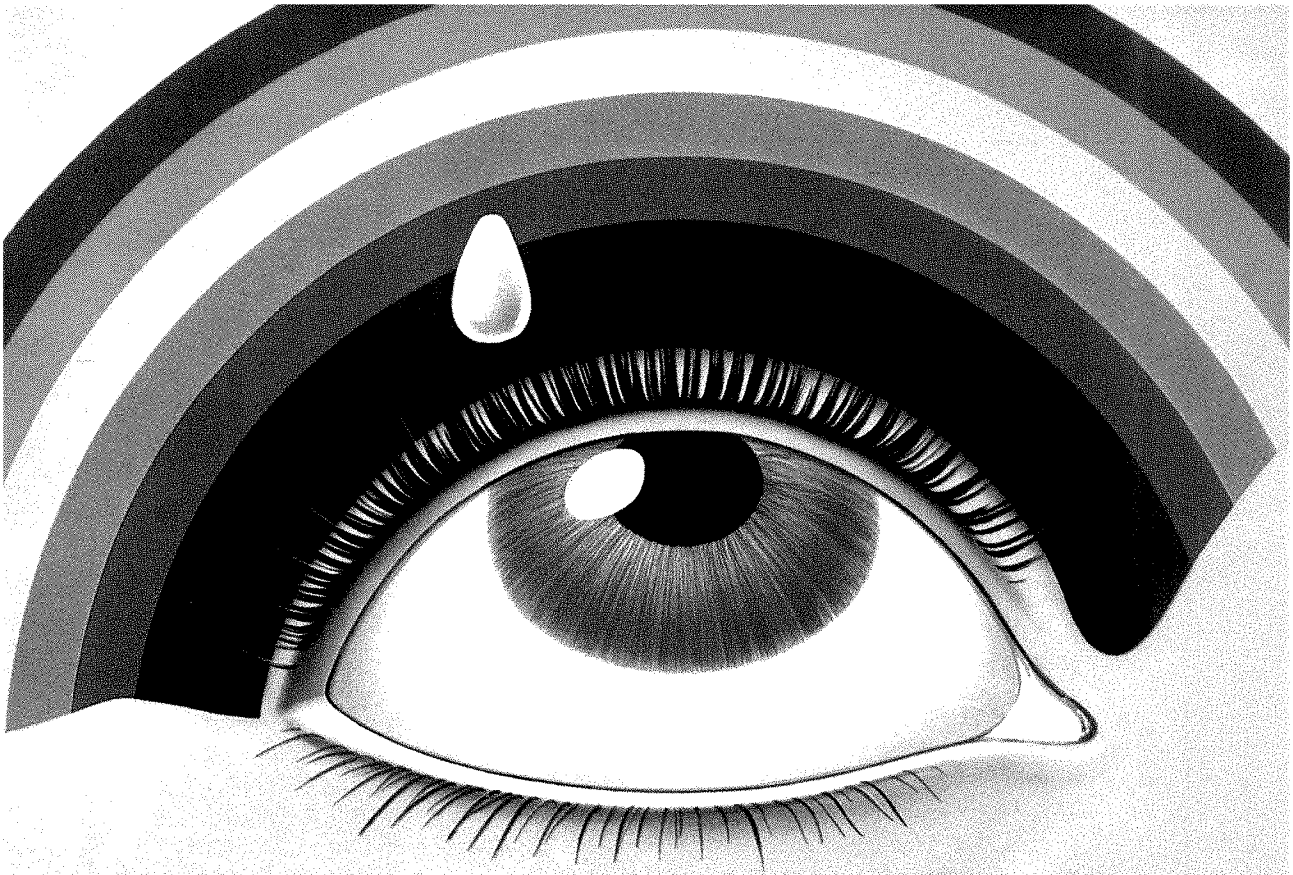

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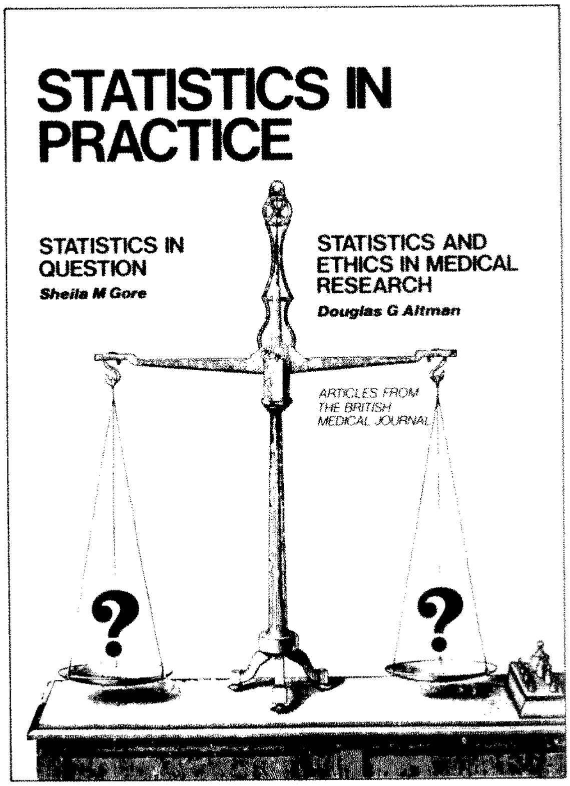

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July 1982 Vol. 66 No. 7

British Journal of Ophthalmology

BRITISH MEDICAL ASSOCIATION TAVISTOCK SQUARE LONDON WC1H 9JR

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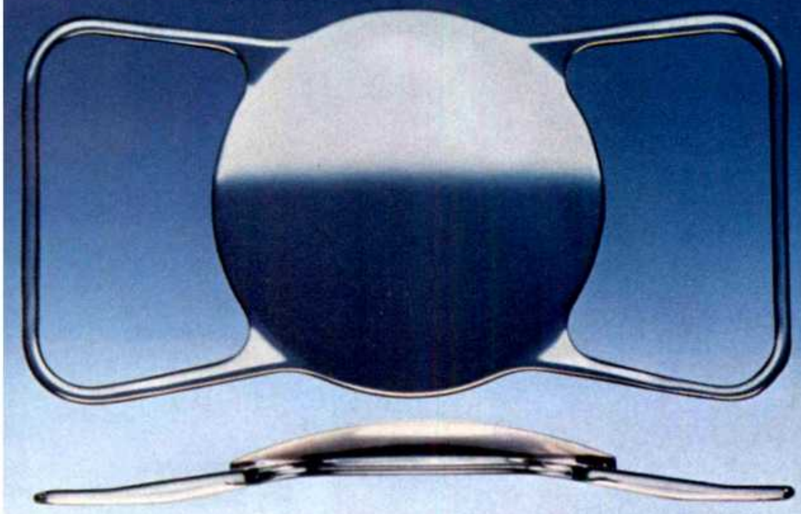

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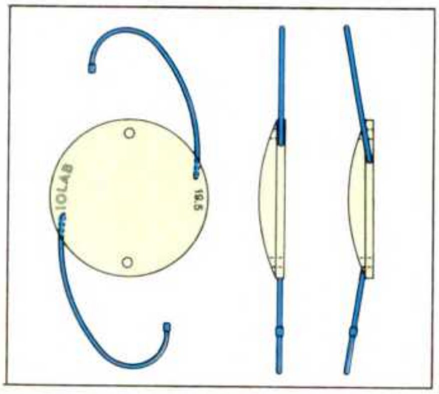

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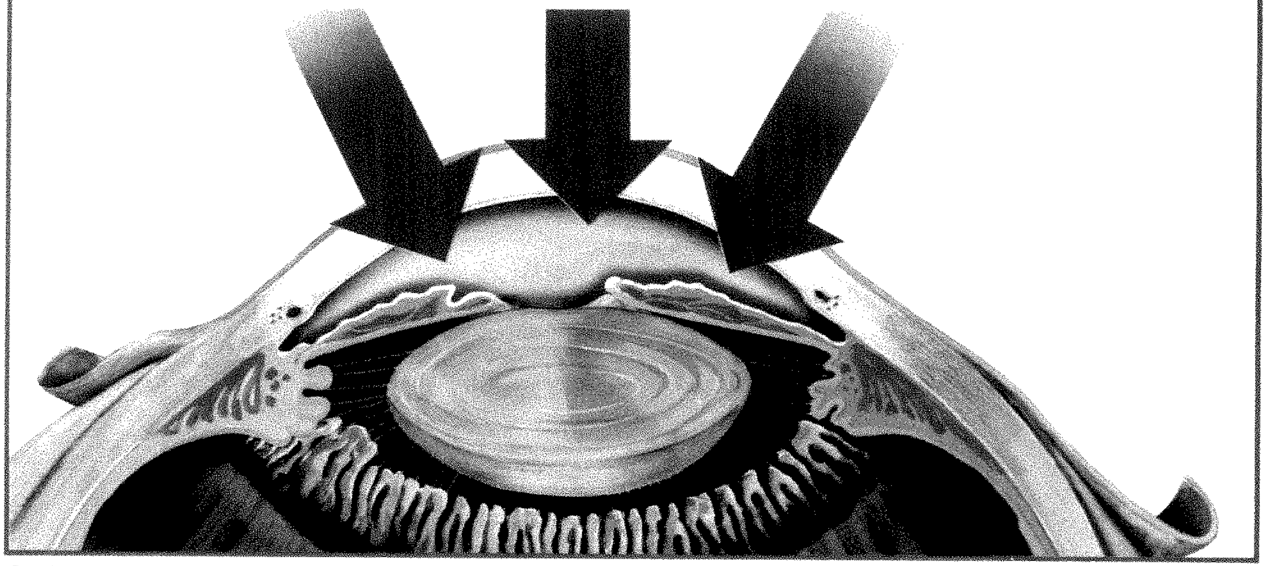

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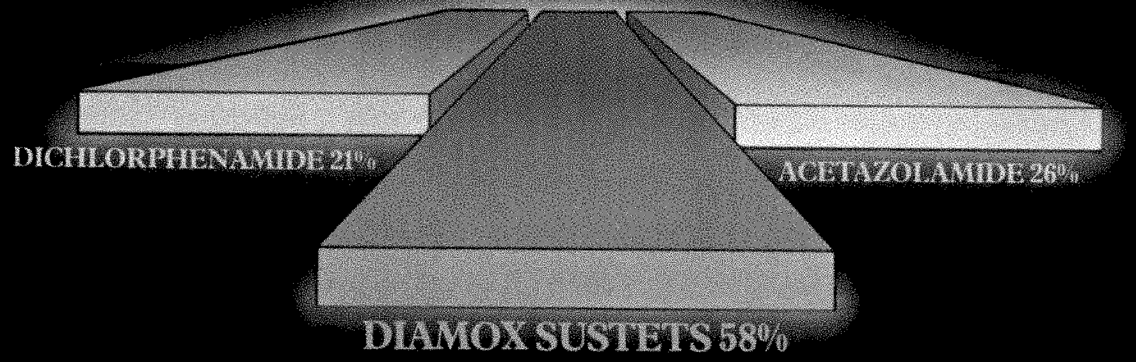

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British Journal of Ophthalmology, 1982, **66**, 405–416

On the heredity of retinitis pigmentosa

MARCELLE JAY

From Moorfields Eye Hospital, City Road, London EC1V 2PD

SUMMARY The aims of this study are: (1) to determine the frequencies of the various genetic forms of retinitis pigmentosa; and (2) to perform segregation analysis on autosomal dominant, autosomal recessive, and X-linked families. The families studied consisted of 2 series of patients at Moorfields Eye Hospital: (1) 426 families seen in the Genetic Clinic; and (2) 289 families seen in the Electrodiagnostic Department. Comparison between the 2 series identified biases of ascertainment, and it was estimated that the combined series included 53% of simplex cases and a minimum of 15% of X-linked families. Segregation analysis of the Genetic Clinic series showed good agreement with expectation in autosomal dominant and X-linked families, but indicated that no more than 70% of all simplex cases were autosomal recessive. The rest of the simplex cases were mildly affected and may represent fresh autosomal dominant mutations, autosomal dominant transmission with reduced penetrance, the heterozygous state of X-linked disease in some of the females, and phenocopies.

> Many years ago a well dressed man who looked in excellent health, came to my desk in the out-patient room, at Moorfields, and in a somewhat excited manner declared 'I am going blind Sir! you can do nothing for me I know! It is in the family, and has been for centuries, and at the present time I know more than thirty who are either blind or on the way to it. When once it begins it always goes on; still I should be glad if you would look at my eyes.' I did so and found, as I expected, that he was the subject of retinitis pigmentosa.[1]

The early authors classified the different genetic forms of retinitis pigmentosa using much the same system as did Nettleship[2] in defining heredity in his series. Three main categories were recognised: (1) continuous, with direct inheritance in an unbroken line; (2) discontinuous, with parents normal but affected aunts, uncles, cousins, or grandparents; (3) collateral, where the parents were normal but sibs were affected. A fourth group consisted of cases inherited from both parents, when the heredity was termed double or reinforced.

In modern terminology the first group corresponds to autosomal dominant transmission; the second might be autosomal recessive, X-linked, or autosomal dominant with reduced penetrance depending on the pedigree; and the third group probable autosomal recessive. It is very difficult, however, to analyse either the Nettleship[2] or Bell[3] series of pedigrees, as insufficient information is available.

Since 1925 the genetics of retinitis pigmentosa have been studied extensively in Europe,[4–10] and as a result the autosomal recessive mode of transmission has been considered to be the most common.[11–20] The significance of X-linked transmission in retinitis pigmentosa was probably recognised intuitively by Nettleship (1845–1913), and there are numerous examples of this mode of transmission in the early literature.[21–30] The most significant findings, particularly in the recognition of the carrier state in the female heterozygote, were by Falls and Cotterman[23] and by Bird.[31]

There have been several studies since 1961 comparing the proportions of the different genetic forms of retinitis pigmentosa in various parts of the world: Switzerland[4 5] Belgium,[8 32] Israel,[33] Japan,[30 34 35] the USSR,[36] the United Kingdom,[9 37 38] and the USA.[39–41] Some of these studies were based on clinical and hospital records, and others were obtained from various samples of well-defined populations. The proportions of the different genetic forms vary from one series to another, and they reflect the ethnic and other socioeconomic factors which influence the prevalence of any genetically determined disease in a given population (Table 1).

Consanguinity rates vary: in Switzerland and in Israel they are relatively high, whereas in Japan[30] they

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Correspondence to Dr Marcelle Jay.
Part of a thesis accepted by the University of London for the degree of PhD.

Table 1 *Frequency of different genetic forms*

Author	*AD*	*AR*	*XL*	*Sp*	*No. of cases*
Ammann *et al.*[4]	9%	90%	1%		153
Boughman[39]	10%	81·1%	8·9%		608
Fishman[40]*	26%	19%	16%	38%	173
François[8]	19·5%	37%	4·5%	39%	?
François and Verriest[44]	19%	35%	4·1%	41·3%	153
Imaizumi[47]	2·1%	40·1%		43·2%	1091
Jay[9]	39%	15%	25%	21%	77
Jay[37]	38·7%	17%	23·6%	20·7%	106
Jay[38]	39%	15%	25%	21%	300
Motohashi[35]				83%	519
Panteleeva[36]	12·7%	27·9%	1·1%	?	678
Pearlman *et al.*[41]	5·9%	13·2%	7·4%	73·5%	68
Tanabe[30]: group A		54·6%			1650
group B		64·7%			839

*The remaining 1% was of undetermined genetic type. AD=autosomal dominant. AR=autosomal recessive. XL=X-linked. Sp=sporadic.

are low and similar to those in the UK[42] and in the USA.[39] The sex ratio, from which calculations of an expected proportion of X-linked cases can be made, is not always indicative of the true distribution of X-linked disease. In the USSR, for example, there was a significant excess of female probands (415 females to 263 males). Such an excess of female probands is a bias of ascertainment which might surprise an ophthalmologist, but is a common experience of clinical geneticists.

The aims of the present study are to determine the frequencies of the different genetic forms of retinitis pigmentosa, to perform segregation analysis where possible, and to analyse certain factors which are relevant to genetic counsellors faced with a patient in whom the diagnosis of retinitis pigmentosa has been established.

Patients and methods

The patients in this study were drawn from 2 different sources and form separate groups.

(1) 426 families with retinitis pigmentosa were seen in the Genetic Clinic of Moorfields Eye Hospital in the period from July 1969 to August 1979 (and this series will be referred to as the GC series). Patients in these families were referred mainly from general clinics within the hospital, though a number were referred from other hospitals or from general practitioners. They do not, however, represent every case of retinitis pigmentosa seen within the hospital during this period. Their referral was usually for assessment, for genetic counselling, or stimulated by the various research projects being carried out in the Genetic Clinic, and patients in this series were seen by one of 3 clinicians.

(2) The Electrodiagnostic Department of Moorfields Eye Hospital has been in existence since 1964, and approximately 8500 patients were referred to the department up to August 1979. Their sources of referral are from general clinics within the hospital and from consultants at other hospitals. A search through these records yielded 289 families not previously known to the Genetic Clinic, which form a group called the ED series. A high proportion of these patients were referred to the department for diagnostic purposes.

The GC series and the ED series probably represent the majority of patients with retinitis pigmentosa who have been seen at Moorfields Eye Hospital, though this combined series does not represent complete ascertainment.

METHOD OF RECORDING THE DATA

Every family was recorded on special Genetic Clinic notes, which included a full family history, a record of the pedigree, and clinical information. The data recorded include name, address, date of birth, hospital and series numbers, nationality, race, religion, pedigree (with space for dates of birth of relatives), and consanguinity. The occupation was sometimes recorded. Individual members of families were entered into a computerised index with the following attributes concerning each entry: Surname, maiden name, initials, series number, sex, year of birth, mode of transmission, clinical status, area of origin.

CRITERIA FOR MODE OF TRANSMISSION

The mode of transmission was divided into a number of categories which could be either grouped together or considered separately for various analyses. The criteria for autosomal dominant transmission were: similar clinical manifestations in males and females; 2

or more generations of direct transmission; and preferably, but not necessarily, father-to-son transmission.

For the purpose of this study the criteria for autosomal recessive transmission were either evidence of parental consanguinity, or the affected individual had parents who were believed to be homozygous or heterozygous for autosomal recessive retinitis pigmentosa on the basis of the family history. Families satisfying these criteria were labelled 'probably autosomal recessive.'

Other families were recognised as being possibly autosomal recessive, and these were either multiplex (2 or more affected sibs) or simplex (one affected member in a sibship). The multiplex were divided into 2 groups: (*a*) male only affected, which could be autosomal recessive or X-linked and termed 'male multiplex'; and (*b*) male and female affected or only females affected, termed 'mixed multiplex.' All the simplex cases (without parental consanguinity) were also recognised as being possibly autosomal recessive but were further subdivided according to clinical criteria of age and severity of the disease[43] into the following categories: clinically autosomal dominant (mildly affected); clinically autosomal recessive (severely affected females); clinically autosomal recessive or X-linked (severely affected males); uncategorised (intermediate in severity).

X-linked transmission in the GC series was evident from the pedigree and from the examination of heterozygotes, but evidence of an affected male maternal relative and an apparently unaffected mother was taken to be sufficient to assume X-linked inheritance in the ED series. A further category labelled 'transmission unknown' was assigned to those few families where, although there was more than one affected member, the mode of transmission could not be deduced from the pedigree.

The attribute of clinical status was divided into: affected, obligate heterozygote, possible heterozygote unaffected, unknown, and possibly affected. The category 'unaffected' has been kept exclusively for parents of simplex cases and of all multiplex cases, other than those considered to be probably autosomal recessive. The category 'unknown' usually refers to the members of early generations in the autosomal dominant or X-linked families, and the 'possibly affected' is an at-risk category used for children of affected subjects with autosomal dominant or X-linked inheritance.

The code for area of origin was based on a variant of the system used by the regional health authorities for the various counties.

The index has been used primarily for identifying families and comparing surnames in pedigrees. There is in addition another file of the common and duplicated surnames occurring in the main index. The data in the computer are revised at regular intervals and updated whenever additional information becomes available.

Results and discussion

GENETIC CLINIC SERIES

Distribution of probands. The Genetic Clinic series consists of 426 families in which a firm diagnosis of retinitis pigmentosa has been made. The distribution of families, probands, and total number of affected subjects according to genetic form is shown in Table 2. The proportion of X-linked families, which has always been higher than in any other series in the literature, is identified clinically as 15·7%, and this group has a large number of obligate heterozygotes among the probands.

The number of apparently unaffected probands was 9·6% of the total and reflects the concern of asymptomatic subjects who have affected relatives for the implications to their own children. This is particularly relevant for women and is illustrated in the X-linked families, in which between one-quarter

Table 2 *Number and sex distribution of families, probands, and affected subjects according to genetic form in GC series*

Transmission	*Families*		*Probands*				*Total No affected*	
	Number	*%*	*M*	*F*	*m*	*f*	*M*	*F*
AD	104	24·4	30	63	3	8	211	228
Probably AR	29	6·8	17	11	1	1	25	22
X-linked	67	15·7	44	—	4	19*	189	187*
Mixed multiplex	28	6·6	5	23	1	3	27	42
Male multiplex	19	4·5	16	—	2	2	44	—
Simplex	175	41·1	103	72			103	72
Adopted	4	0·9	2	2			2	2
Totals	426		217	171	11	33	601	553

*Eighteen of the 19 probands were identified as heterozygotes, and all the 'affected' females were heterozygotes.
M=affected male. F=affected female. m=unaffected male. f=unaffected female.

Table 3 *Sex distribution of simplex cases in the GC series according to clinical severity*

	Males	*Females*	*Totals*
Clinically AR (severely affected	31	15	46
Clinically AD (mildly affected)	27	23	50
Unclassified (intermediate in severity)	45	34	79
Totals	103	72	175

and one-third of these families were ascertained through the females, and where 18 out of 19 women were discovered to be heterozygotes. The large number of female probands in the X-linked families is undoubtedly related to the demand for genetic counselling in severe disease. It is also possibly a consequence of the well-publicised research interest of the clinicians at Moorfields Eye Hospital.

The proportion of simplex cases is 41·1%, and their division according to clinical form is shown in Table 3. There are 9 male and 8 female simplex cases among the probands in the autosomal recessive group, and if all simplex cases with or without parental consanguinity are considered as a group there are 112 male and 80 female simplex cases. The excess of males in this group is statistically significant ($\chi^2=5{\cdot}33$, $p<0{\cdot}02$). Similarly, if all simplex and multiplex cases, with or without consanguinity are grouped together, there is a total of 172 affected males and 113 affected females. The deviation from the expected sex distribution is highly significant ($\chi^2=12{\cdot}21$, $p<0{\cdot}01$).

There is a significant excess of females among the probands in the autosomal dominant families (63 females to 30 males), but the excess of females among all affected members of the same group is no longer significant (228 females to 211 males), indicating a bias of ascertainment in this group. This may be due to various factors such as the economic implications of occupation which may weigh more heavily on men than on women. Women may be more prone than men to seek specialist advice on prognosis and possible treatment, and they appear more likely to seek genetic counselling.

Comparison of frequency of genetic forms. The frequency of the various genetic forms differs when calculated as a proportion of the families on the one hand, and as a proportion of the total number of affected individuals in the pedigree on the other. The proportion of autosomal dominant disease is much higher (38%) among affected individuals than among families, where it is 24·4%. Similarly, the X-linked proportion is 15·7% among families and 32·6% among affected individuals. This clearly illustrates the bias which is introduced when a series is based on affected individuals with a positive family history.

The frequency of autosomal dominant retinitis pigmentosa among families (24·4%) is much lower than the 39% found in previous studies.[9, 37, 38] This may be the result of a different division of the series or of the relatively higher proportion of X-linked and simplex cases in the present series. The proportion of autosomal dominant disease in the present study is comparable to 2 other studies: François[8] found 19·5%, and Fishman[40] found 26%.

The frequency of autosomal recessive retinitis pigmentosa is 6·4%, which does not take into account all the simplex and multiplex cases which may be recessive after removal of the X-linked proportion, and this topic will be discussed in the light of the results of segregation analysis.

The estimation of the frequency of genetic forms among families shows that the proportion of simplex cases is slightly higher than in a previous study based on 305 families.[43] This may be due to more generalised referral from various sources or from a greater demand by patients for assessment and counselling.

Estimation of X-linked form in simplex and multiplex sibships. A method suggested by Fraser[45] was used to estimate the X-linked proportion in these groups, based on the comparison of sibships with affected members of one sex only. With autosomal recessive inheritance there should be as many sibships of males only affected as of females only affected. The defined autosomal recessive sibships are removed from the analysis, and the excess of sibships with only males affected can be directly attributable to X-linked inheritance. Furthermore a sibship with, for example, 3 affected children may be distributed in 4 different combinations: 3 males, 3 females, 2 males and 1 female, or 1 male and 2 females. If n_k is the number of sibships other than male only affected with k affected members, then the number of sibships with only male affected is:

$$\frac{n_k}{2^k-1}.$$

This calculated number of sibships is compared with the observed number of sibships with only males affected, and the excess corresponds to the number of sibships which may be attributable to X-linked transmission. This excess may also be converted to a simplex number of X-linked cases by multiplying it by the simplex:multiplex ratio obtained from the autosomal recessive group. These methods will give an approximation of the proportion of X-linked cases, and they have been applied to all multiplex families in the GC series (Table 4). The results showed that 11·76 out of the 19 male multiplex sibships in this series could be attributable to

Table 4 *Expected/observed proportion of male multiplex sibships in GC series*

No. of affected	*No. of mixed multiplex*	*Male only affected*		
		Expected	*Observed*	*Excess*
2	18	6·00	14	8·00
3	8	1·14	4	2·86
4	1	0·07	1	0·93
5	1	0·03	0	−0·03
Totals	28	7·24	19	11·76

Affected of one sex only		*Affected of both sexes*	
Male	*Female*	*Male*	*Female*
44	14	27	28

X-linked transmission. Of the 19 male multiplex sibships there were 12 where the mother was unavailable for examination, and in 8 of these there were no daughters. The daughters in the remaining 4 sibships were under the age of 10 years and no abnormality could be detected in them.

The simplex:multiplex ratio among the 'probably autosomal recessive' group is 17:12, and, if it is assumed that the same ratio may be applied to the excess of male multiplex sibships, the estimated number of simplex cases with X-linked transmission is between 16 and 17 (16·66). If a minimum of 16 males are deducted from the 76 males (simplex cases other than mildly affected), the remaining 60 males may be compared with the 49 females of the same clinical status, and the excess of males is no longer statistically significant ($\chi^2=1{\cdot}11, 0{\cdot}2<p<0{\cdot}3$).

The proportion of X-linked families, which has always been higher than in any other series in the literature, is identified clinically as 15·7% and has been calculated as 22·3% (95/426). There appears to be a large proportion of sibships which were presumably not identified as being X-linked by examination of the heterozygote or the recognition of the phenotype of the isolated hemizygote. Although every effort is usually made to examine the possible obligate heterozygotes where X-linked disease is suspected, there are inevitably some cases where the mother is not available, or where the existing daughters are too young for tests to be conclusive. This does not exclude the possibility of subsequent changes in the identified status of these girls, but illustrates the clinical problems in the detection of the heterozygous state and the difficulties in making the correct genetic diagnosis at the time of ascertainment. Similarly, the estimation of 16 out of 76 simplex males with severe or moderately severe disease as being X-linked shows that the hemizygous phenotype is not identifiable clinically in the absence of a corroborative family history.

X-linked retinitis pigmentosa was the subject of a detailed study at Moorfields Eye Hospital,[31] and it is possible that a high proportion of X-linked families in the country has now been ascertained, in contrast to autosomal dominant families, where the disease is milder and ascertainment less complete. The number of patients with identifiable X-linked retinitis pigmentosa is still rising, but many of these belong to families already ascertained. There are also one or 2 instances in which 2 or 3 small X-linked pedigrees have been found to be parts of one large pedigree, and presumably this occurrence will become more common with time.

The relatively high proportion of X-linked retinitis pigmentosa in this series may be due to the higher prevalence of this form of the disease in this country than in others. A study in the USA in a series of comparable size[39] identifies the proportion of X-linked as 8·9%, the data being derived from a questionnaire. However, in view of all the clinical problems of the identification of this form, the proportion of X-linked retinitis pigmentosa in the USA may well be considerably higher than 8·9%. Unfortunately, the extensive study in Japan[30] gave no indication of the proportion of the X-linked form.

Another reason for the high proportion of X-linked retinitis pigmentosa in this study is the high referral rate, which results from several factors. These include: the occurrence of severe disease in several generations (and in some families with many affected members); the known interest of clinicians at Moorfields Eye Hospital in X-linked disorders; and the observation that a number of obligate heterozygotes have deduced the mode of inheritance of the disorder in their families, and have requested genetic counselling and advice on the prognosis of the disease not only for themselves but often for their children. It is also evident that the clinical identification of heterozygotes may be difficult, particularly when they are young and the fundus changes may be minimal.

ELECTRODIAGNOSTIC SERIES

Distribution of probands. The electrodiagnostic series consists of 289 families in which a tentative diagnosis of retinitis pigmentosa was made by a clinician from a general clinic at Moorfields Eye Hospital or from another hospital and patients were referred to establish a diagnosis. The distribution of families and probands according to genetic form and sex is shown in Table 5. The sex distribution among probands in all simplex and multiplex cases with or without consanguinity is 142 males and 90 females. The deviation from the expected sex ratio is highly significant ($\chi^2=11{\cdot}66$, $p<0{\cdot}01$), and consistent with a

Table 5 *Number and distribution of probands according to genetic forms in the ED series*

Transmission	*No. of families*	*%*	*Probands*	
			Males	*Females*
AD	43	14·9	19	24
Probably AR	4	1·4	2	2
X-linked	11	3·8	9	2
Mixed multiplex	13	4·5	7	6
Male multiplex	12	4·2	12	—
Simplex	203	70·2	121	82
Adopted	3	0·9	1	2
Total	289		171	118

proportion of clinically unidentifiable X-linked cases similar to that calculated in the GC series.

Frequency of genetic forms. This series differs from the Genetic Clinic series in the manner in which it was ascertained. The cases in this series were referred solely for diagnosis; they do not include those patients previously ascertained in the Genetic Clinic, and there is therefore a bias in favour of cases without a family history. This bias is reflected in the high proportion of simplex cases (70·2%) and the low proportion of autosomal dominant (14·9%) and of X-linked families (3·8%). The whole structure of the Electrodiagnostic Series is predominantly clinically orientated and in the context of this study can only indicate the possible sources of bias in the Genetic Clinic series.

COMBINED MOORFIELDS EYE HOSPITAL SERIES

Despite the fact that reliable family details are incomplete in the ED series it is interesting to consider the GC and the ED series together. The bias towards cases with a positive family history in the GC series is compensated by the bias towards simplex cases in the ED series, and the combined Moorfields Eye Hospital (MEH) series is more representative of the hospital population, even although it does not include every patient with retinitis pigmentosa seen at Moorfields Eye Hospital.

The MEH series contains 715 families with retinitis pigmentosa, and there are 378 simplex cases without parental consanguinity, a proportion of 52·9%. Few other series in the literature have a comparable number of families except Boughman,[39] where the data showed that 161 (44·1%) were simplex families and the remainder were multiplex. Nettleship[46] found 50% of simplex cases in his series of 1381 cases, and Imaizumi[47] found 43·2% of sporadic cases in a series of 1091 cases. The proportion of simplex cases in the MEH series among the total number of affected individuals, as distinct from families, is lower than 52·9%.

The proportion of autosomal dominant families in the MEH series is 20·6%, which is comparable to the 19·5% found by François[8] but approximately half the proportion found in previous studies on patients attending the Genetic Clinic.[9 37–38] The relative frequencies of X-linked and autosomal recessive families depend on calculations which cannot be applied to the ED series, although it can be seen that there is a minimum of 15% (106/715) X-linked families in the combined series. This proportion is probably very similar to the 16% found by Fishman[40] in a much smaller series of 173 cases, but is lower than the consistent value of 25% found in previous studies on patients from the Genetic Clinic.[9 37 38]

It is tempting to speculate to what degree the proportion of 52·9% of simplex cases and a minimum of 15% of X-linked families in the MEH series is representative of the population in the country as a whole. Moorfields Eye Hospital has a special status. It is not solely a secondary referral hospital, for its has both a large general outpatient department and a large casualty department with an 'open door' policy, and 249 312 outpatients were seen in the 2 branches of the hospital in 1978.[48] A large proportion of the outpatients are referred from general practitioners, and a significant proportion live outside London.

Although there is provision for race and religion on the special Genetic Clinic notes, these are not invariably recorded. It is apparent from the limited data available, and from the number of consanguineous marriages among Muslims and Hindus, that the immigrant population in south-east England is represented in the GC series, although their exact proportion is not known. The Electrodiagnostic Clinic is even more cosmopolitan in the ethnic origin of its patients. Similarly, the patient's occupation or profession is not always recorded. It seems, however, from the data which are available that retinitis pigmentosa is no respecter of social class and that it is not more prevalent among the so-called deprived sector of the community.

All the evidence indicates that the proportion of 52·9% of simplex cases without parental consanguinity, and a minimum of 15% of X-linked families, may be representative of the population of south-east England. The frequency of X-linked disease is related to families and not cases, and the families are drawn from the whole of England and Wales, with no evidence so far of any clustering in a particular region. It must be concluded that X-linked retinitis pigmentosa is a relatively common form of the disease throughout this country.

SEGREGATION ANALYSIS OF GENETIC CLINIC SERIES

Segregation analysis was performed only on the

Genetic Clinic series, where the family structure was known in all but a few cases.

Possible autosomal recessive families. All known autosomal dominant, X-linked, and adopted families were removed from the group for analysis, and the remainder consisted of: the probably autosomal recessive group; all the multiplex cases; and all the simplex cases. (Male-only multiplex sibships were included, since even those which may be X-linked do not affect the segregation ratio.)

Various methods of segregation analysis are available.[49–51] A number of these depend on complete ascertainment and cannot therefore be applied to this series. The method of choice is that described by Crow[52] and is an adaptation of earlier methods.[53 54] This method is similar to the Weinberg 'proband' method but adapted for use in multiple incomplete ascertainment. A first approximation of the segregation ratio p_0 is estimated by obtaining the ratio of affected sibs to the total number of sibs of probands for the pooled families.

If a=number of probands
s=sibship size
r=number of affected
then

$$p_0=\frac{\Sigma a\,(r-1)}{\Sigma a\,(s-1)}$$

A parameter (π), known as the probability of ascertainment is calculated from the equation

$$\pi=\frac{\Sigma a\,(a-1)}{\Sigma a\,(r-1)}$$

The corrections suggested by Crow[52] consist of a correction factor C defined by

$$1/C=1+\pi+p_0\pi(s-3)$$

which is applied to calculate a more accurate value of the segregation ratio p where

$$p=\frac{\Sigma Ca\,(r-1)}{\Sigma Ca\,(s-1)}$$

The effect of C is to reduce the contribution from the larger sized families, so that p is greater than p_0.
The variance V_p is given by

$$V_p=\frac{p\,(1-p)}{\Sigma Ca\,(s-1)}$$

Crow[52] also suggested calculating the 2 limiting values of p, corresponding to truncate selection where $\pi=1$, and single selection where $\pi=0$. The value of p for truncate selection is the upper limiting value, and the value of p for single selection is the lower limiting value of the segregation ratio.

The clinical division of simplex cases into groups which were clinically autosomal dominant (with mild disease) or autosomal recessive (with severe disease) provided a basis for a similar division for the purpose of segregation analysis. The methods outlined above were therefore used on 3 groups depending on the selection of simplex cases included. Group 1 consisted of all multiplex sibships, all probably autosomal recessive families, and all simplex cases whatever the clinical category. Group 2 was similar to group 1 except that the simplex cases which were clinically autosomal dominant were excluded. And group 3 was also similar to group 1 except that only those simplex cases which were clinically autosomal recessive were included. The results of segregation analysis on the 3 groups of possibly autosomal recessive families are summarised in Table 6. The value of the segregation ratio varied according to the methods used, with single selection giving low values, truncate selection giving high values, and multiple selection giving intermediate values. Similarly, group 2 which included simplex cases which were clinically autosomal recessive or unclassified consistently gave intermediate values of the segregation ratio. Low values were obtained for group 1 and high values for group 3.

Since the distribution of simplex cases in the GC series was a deciding factor in the estimation of the segregation ratio, the equation derived by Morton[55] and Morton and Chung[56] in studies of muscular dystrophy was used to estimate the proportion of sporadic cases or phenocopies. According to Morton, if x is the proportion of sporadics among the simplex cases, and s, p, and π are as previously defined, then the distribution P of families with one affected member is given by:

$$P=\frac{sp\pi[x+(1-x)q^{s-1}]}{xsp\pi+(1-x)\,[1-(1-p\pi)^{s}]}$$

P is calculated by using 2 trial values of x for every value of s, and the expected number of sibships with one affected member is obtained from the calculated values of P. The value of x is then obtained by linear interpolation.

Table 6 *Summary of results of segregation analysis of autosomal recessive families in GC series*

Method	*Group 1*	*Group 2*	*Group 3*
Multiple selection	p=0·135	p=0·170	p=0·263
	σ=0·014	σ=0·018	σ=0·025
Single selection	p=0·122	p=0·155	p=0·243
	σ=0·013	σ=0·016	σ=0·023
Truncate selection	p=0·243	p=0·283	p=0·383
	σ=0·021	σ=0·024	σ=0·039
Proportion of sporadics	x=0·285	x=0·104	x=−0·371

The value of p used in this equation was arbitrarily chosen to be the estimated value obtained from multiple selection applied to group 2, which was considered to be the closest to the true figure. The calculation of x, the proportion of sporadics, was made for all 3 groups for purposes of comparison and for some indication of the validity of the assumptions made in their definition. The results show that for group 1 which included all simplex cases, $x=0{\cdot}29$; for group 2, which excluded mildly affected simplex cases, $x=0{\cdot}10$; and for group 3, which included only severely affected simplex cases termed 'clinically autosomal recessive,' $x=-0{\cdot}37$.

Segregation analysis was performed initially on all simplex and multiplex cases, with or without consanguinity, which could be autosomal recessive. The value of the segregation ratio obtained by multiple selection is low with $p=0{\cdot}135$, a finding common to other series.[5 39] While the segregation ratio is expressed as a proportion, it is derived from the summation of affected sibs and the summation of all sibs of probands. A low segregation ratio may therefore be the result of a deficit of multiplex cases and/or an excess of simplex cases.

The deficit of multiplex cases may be due to late age of onset causing belated ascertainment of affected sibs, although this is unlikely, as the mean age of onset in this study was found to be 12·7 years and may well be lower. The mean family size in simplex cases did not differ significantly from that in multiplex cases, and it was therefore considered that the low value of the segregation ratio was due to the large number of simplex cases included in the analysis.

The simplex cases formed a clinically heterogeneous group, and this study has already demonstrated that the phenotype of the hemizygote in X-linked disease is not distinguishable from that of the male with autosomal recessive disease. Similarly, the phenotype of the obligate heterozygote in X-linked disease may not always be distinguished from that of the female with autosomal dominant disease. In the absence of any method demonstrating a measurable enzyme defect in autosomal recessive disease it was assumed that the autosomal recessive phenotype is generally one expressing severe disease. Thus for the purpose of simple segregation analysis the division of simplex cases according to clinical type, as shown on Table 3, was used as a criterion for autosomal recessive transmission.

The values of p obtained for single selection in each group correspond to the case where there is only one proband per family, and those obtained for truncate selection correspond to the extreme case where every affected member is a proband. There were several families with more than 2 affected members, and it would have been most unlikely that they were all independently ascertained. Truncate selection is therefore a limiting case, and it is a useful tool in population genetics, but it does not correspond to the reality of practice at Moorfields Eye Hospital. The most acceptable value of the segregation ratio was that obtained by calculations from multiple selection, and it can be seen from Table 6 that in group 2 the value of p was 0·17 with a standard deviation of 0·018. The value of p therefore lies between 0·15 and 0·20 within 95% confidence limits.

The assumption that all simplex cases in this series are not all autosomal recessive was further tested by using a statistical probability function. This function was derived from a study of muscular dystrophy[56] and is used to calculate the proportion of 'sporadic' or nongenetic among simplex cases. It was applied to the data of the GC series based on a segregation ratio of $p=0{\cdot}17$, and the results confirmed a few assumptions previously made. In group 1, which included all 175 simplex cases, the proportion of sporadic cases was 28·5% (50/175). When this number was adjusted for the calculated number of 16 X-linked cases, the number of sporadic cases in group 1 was 34, or a proportion of 19·4%. In group 3 there were manifestly too few simplex cases included, which led to a negative value for the proportion of sporadic cases. The most interesting result was in group 2, where the proportion of sporadic among the 125 simplex cases was 10·4% (13 cases). This result implies that after removal of the X-linked cases there were no sporadic cases or phenocopies in group 2.

The genetic status of the group of 50 simplex cases termed 'clinically autosomal dominant' is a matter for discussion. A number of females within this group may be X-linked heterozygotes, because the carrier state in X-linked disease is not always identifiable by the methods at present in use in the absence of a typical pedigree. A certain number of males and females within this group may represent fresh autosomal dominant mutations. The data on parental age in this group are incomplete and the ages are not corrected for parity, but there are, however, 9 instances where the age difference between spouses is equal to or greater than 7 years. These results indicate that there may be some fresh autosomal dominant mutations in this group. Nevertheless the results of mathematical analysis alone imply that there may be as many as 34 (19·4%) sporadic cases or phenocopies among the total number of simplex cases.

By definition this group of 'clinically autosomal dominant' cases has a relatively late onset of mild disease, and the parents are frequently not available for examination. It is possible that a certain number of these parents may have been subclinically affected or even that the grandparents may have been mildly affected. Some of these cases may therefore represent a group of autosomal dominant retinitis pigmentosa with or without reduced penetrance, with a small number of fresh autosomal dominant mutations. It is also possible that a number of these mildly affected simplex cases are clinically unidentifiable phenocopies.

The statistical analysis has shown that out of 175 simplex cases it may be assumed that 109 are autosomal recessive and 16 are X-linked males. The remaining 50 are mildly affected, and some of these may be fresh autosomal dominant mutations. The remainder may be X-linked heterozygotes, autosomal dominant cases whose parents have escaped detection, or possibly clinically unidentifiable manifesting heterozygotes, or phenocopies. While it is possible that a few of these mildly affected simplex cases are autosomal recessive, the results of segregation analysis indicate that this group, if it exists, is small.

Autosomal dominant families. The method used was that given by Emery.[49] The number of normal and affected offspring of all affected by normal matings is compared with the expected number and a χ^2 test is applied to the deviation from the expected 1:1 ratio. The segregation ratio is the number of affected offspring to total number of offspring, and the penetrance is the ratio of the calculated to theoretical value of the segregation ratio. The segregation ratio for the autosomal dominant families was found to be p=0·453, indicating a penetrance of 90·6%. There were in fact 12 pedigrees out of a total of 104 (11·5%) showing reduced penetrance.

X-linked families. The method used was that given by Emery[49] for X-linked recessive inheritance, since no pedigree in the GC series fulfilled the criteria for X-linked dominant transmission. The method used was similar to that used for autosomal dominant inheritance, except that the segregation ratio in this case was the number of affected sons to the total number of sons. There was the added condition that only the male offspring of obligate heterozygotes were considered. This condition would have restricted the number of informative sibships to such a degree that it was decided to consider the whole pedigree in the calculations and not merely the proband's generation.

The segregation ratio for X-linked families was p=0·47, which is in good agreement with the theoretical value. The number of informative families was small, as only the sons of obligate heterozygotes were included in the analysis.

IMPLICATIONS FOR GENETIC COUNSELLING

The Genetic Clinic series remains the basis of this study owing to the unique combination of genetic and clinical information it provides. Every single proband, and numerous relatives of probands, were seen by one or 2 of only 3 clinicians, resulting in a remarkable homogeneity in clinical approach. The main conclusions drawn from the results of the various analyses should be considered in the light of corroborative evidence from the Electrodiagnostic series.

Frequency of genetic forms. The frequency of the different genetic forms in the GC series was identified initially by considering the phenotype and the family history. The estimation of the unidentified X-linked proportion in the series has shown that the phenotype is not necessarily distinguishable from the autosomal recessive phenotype in the hemizygote and from the autosomal dominant phenotype in the heterozygote.

In the group of conditions such as retinitis pigmentosa, where there is genetic heterogeneity and the occurrence of phenocopies, it cannot be presumed that all cases which are not demonstrably autosomal dominant or X-linked are necessarily autosomal recessive. Segregation analysis has demonstrated that autosomal recessive transmission may be assumed in a group defined by a number of criteria. It has been shown that autosomal recessive retinitis pigmentosa usually produces early and severe visual loss. Autosomal recessive disease can be assumed if one or more sib is severely affected, particularly if there is parental consanguinity. A proportion of severely affected male simplex and multiplex cases are X-linked, and in these instances the heterozygotes usually show evidence of being mildly affected, in contrast to the heterozygotes for autosomal recessive disease, who at present cannot be distinguished from normal individuals.

If these criteria are applied to the GC series, then the autosomal recessive group comprises: 29 families with evidence of parental consanguinity; 28 multiplex sibships termed 'mixed multiplex'; 8 multiplex sibships termed 'male multiplex'; 109 simplex cases with severe disease. The total number of families in the above group is 174, which is 40·8% of the GC series.

The frequency of the different genetic forms in the GC series is therefore as shown in Table 7.

Table 7 *Frequency of different genetic forms in the GC series*

	Identified	*Calculated*
Autosomal dominant	24·4%	24·4%
Autosomal recessive	6·8%	40·8%
X-linked	15·7%	22·3%
Mixed multiplex	6·6%	—
Male multiplex	4·5%	—
Simplex	41·1%	—
Adopted	0·9%	0·9%
Total	100·00	88·4%

The remaining 11·6% in the calculated total consists of 50 simplex cases with mild disease whose genetic status is uncertain but most of whom are not autosomal recessive.

Genetic counselling. The genetic counselling of autosomal dominant and identifiable X-linked families is straightforward. The counselling of presumably autosomal recessive families depends on a number of factors and differs in multiplex and simplex cases.

(1) Multiplex cases. Autosomal recessive transmission may be justifiably assumed in sibships where females only are affected, or where males and females are equally severely affected. In sibships consisting only of affected males, and in the absence of parental consanguinity, X-linked transmission should always be suspected and every effort made to exclude it by examining obligate or possible heterozygotes.

(2) Simplex cases. The genetic counselling of simplex cases, which account for half the ascertained families, still remains a problem and depends upon various factors such as age, sex, and clinical state. The diagnosis of clinical form is age-dependent and, if the disease is mild, often cannot be made until the patient is in the fourth decade. It can often be made in the second decade when the disease is severe. This can be an important factor in a situation where parents of one affected child are concerned about the risk to further children. It is usually possible to diagnose severe disease when the proband is of childbearing age and wishes to know the risk of transmitting the disease.

Males without parental consanguinity and with severe or moderately severe disease form 74% (76/103) of the total, and, of these, 21% (36/76) are estimated to be X-linked, the remainder being autosomal recessive (79%). When the disease is severe or moderately severe, the ratio of autosomal recessive to X-linked is 4 to 1. The risk of transmitting autosomal recessive disease is very small, as it depends upon the frequency of heterozygotes in the general population. In X-linked disease sons are unaffected but all daughters are obligate heterozygotes. Males with severe or moderately severe disease, whose genetic status is uncertain, have negliglible chance of producing affected children (provided they have not married a relative), but have a 1:10 chance of producing a daughter who is a heterozygote for X-linked disease.

Males with mild disease form the remaining 26% of the total, and the problem of their genetic status is not entirely resolved. They may represent fresh autosomal dominant mutations, autosomal dominant transmission with reduced penetrance, or unidentified phenocopies. Taking into account the 90·6% penetrance in autosomal dominant retinitis pigmentosa and the small incidence of phenocopies, this group of males with mild disease have approximately a 45% chance of producing affected children who will also have the mild form of the disease.

Similarly, females without parental consanguinity and with severe or moderately severe disease comprise 68% (49/72) of the total and may be counselled on the basis that they have autosomal recessive disease. The remaining 32% of the total are females with mild disease, a number of whom may be expected to be obligate heterozygotes for X-linked disease and the others fresh autosomal dominant mutations, autosomal dominant transmission with reduced penetrance, or unidentified phenocopies. In contrast to males in whom X-linked transmission is suspected but cannot be confirmed due to the lack of availability of obligate heterozygotes, a precise diagnosis can usually be established in the females by the time they are of childbearing age. It is usually possible to distinguish clinically between females who are obligate heterozygotes for X-linked disease and those who have autosomal dominant disease. The former have a 50% chance of their sons having severe disease, while the latter have a 45% chance of their children having mild disease.

Comment. The methods of analysis which were used are those currently available, and they are based on some assumptions and conditions which are not always realised in clinical practice. The systematic recording of ascertainments, referrals, and similar data is a prerequisite of a certain type of statistical analysis. It is an approach which is admirably suited to the computerised methods of the present day, but which must serve and not dominate the clinician in the practice of medicine.

It is perhaps apt to end with the observation that after 20 years of collecting families with retinitis pigmentosa Nettleship[2] found that half his cases had no family history and no parental consanguinity. The findings in this study are remarkably similar, but it is hoped that the conclusions which are tentatively submitted will be of some assistance to the clinician in giving genetic advice and to those who continue the research into this disease.

Conclusions

(1) The various phenotypes in retinitis pigmentosa cannot always be easily recognised in the absence of a corroborative family history.

(2) The X-linked form of retinitis pigmentosa is a common form of the disease in England and Wales. It was identified clinically as 15·7% and calculated as 22·3% in the Genetic Clinic series, and it was estimated that a minimum of 15% of families in the

combined Genetic Clinic and Electrodiagnostic series had X-linked disease.

(3) Simplex cases without parental consanguinity constitute 41·1% of families in the Genetic Clinic series and approximately 50% of the combined Genetic Clinic and Electrodiagnostic Clinic series. The results of segregation analysis and clinical heterogeneity indicate that no more than 70% of all simplex cases in the GC series are autosomal recessive.

(4) The criteria for autosomal recessive transmission in retinitis pigmentosa should include severe disease.

(5) The clinical assessment of simplex cases is essential for determining their genetic status. There were 192 simplex cases with or without parental consanguinity in the GC series, and, of these, 50 (26%) were mildly affected with disease resembling autosomal dominant disease in clinical form and progression. It is considered that this is not wholly accounted for by a mild phenotype in autosomal recessive disease, but more probably evidence of fresh autosomal dominant mutations, autosomal dominant transmission with reduced penetrance, the heterozygous state of X-linked disease in some of the females, and phenocopies.

(6) The results in the 2 series reflect a bias of ascertainment inherent in each.

(7) The excess of female probands in the autosomal dominant families in the Genetic Clinic series may indicate a greater concern for the genetic implications of the disease in women than in men.

I thank Mr Barrie Jay and Professor Alan Bird for allowing me access to the notes of the Genetic Clinic and for their clinical assessment of cases in this study. I am grateful to Professor G. B. Arden and Mr J. H. Kelsey for allowing me access to the notes of the Electrodiagnostic Department at Moorfields Eye Hospital. I am also grateful to Mrs Vanessa Hanna for secretarial help.

This research was supported in part by MRC grant No G80/0986/7/N and by a grant from the National Retinitis Pigmentosa Foundation, Inc.

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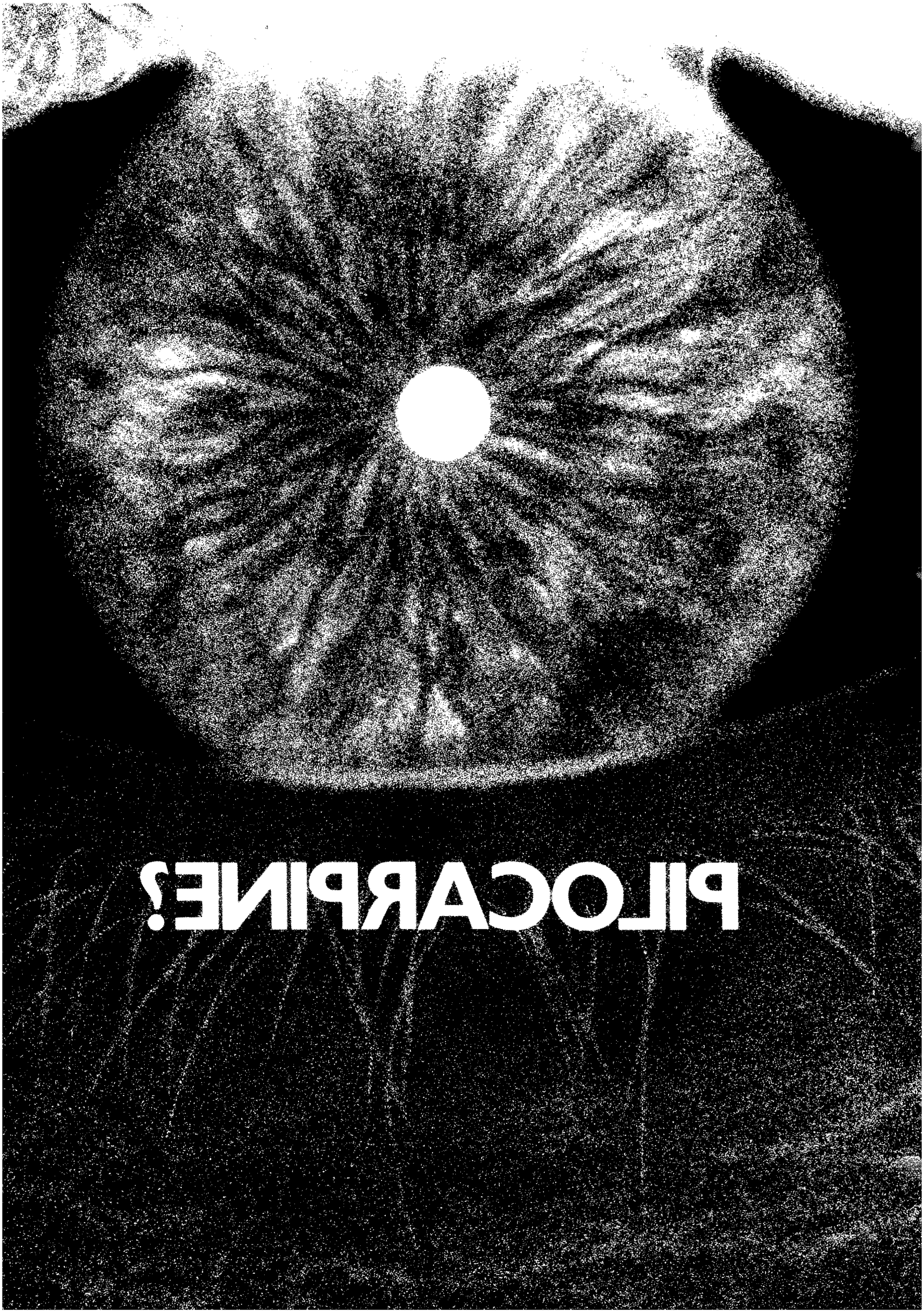
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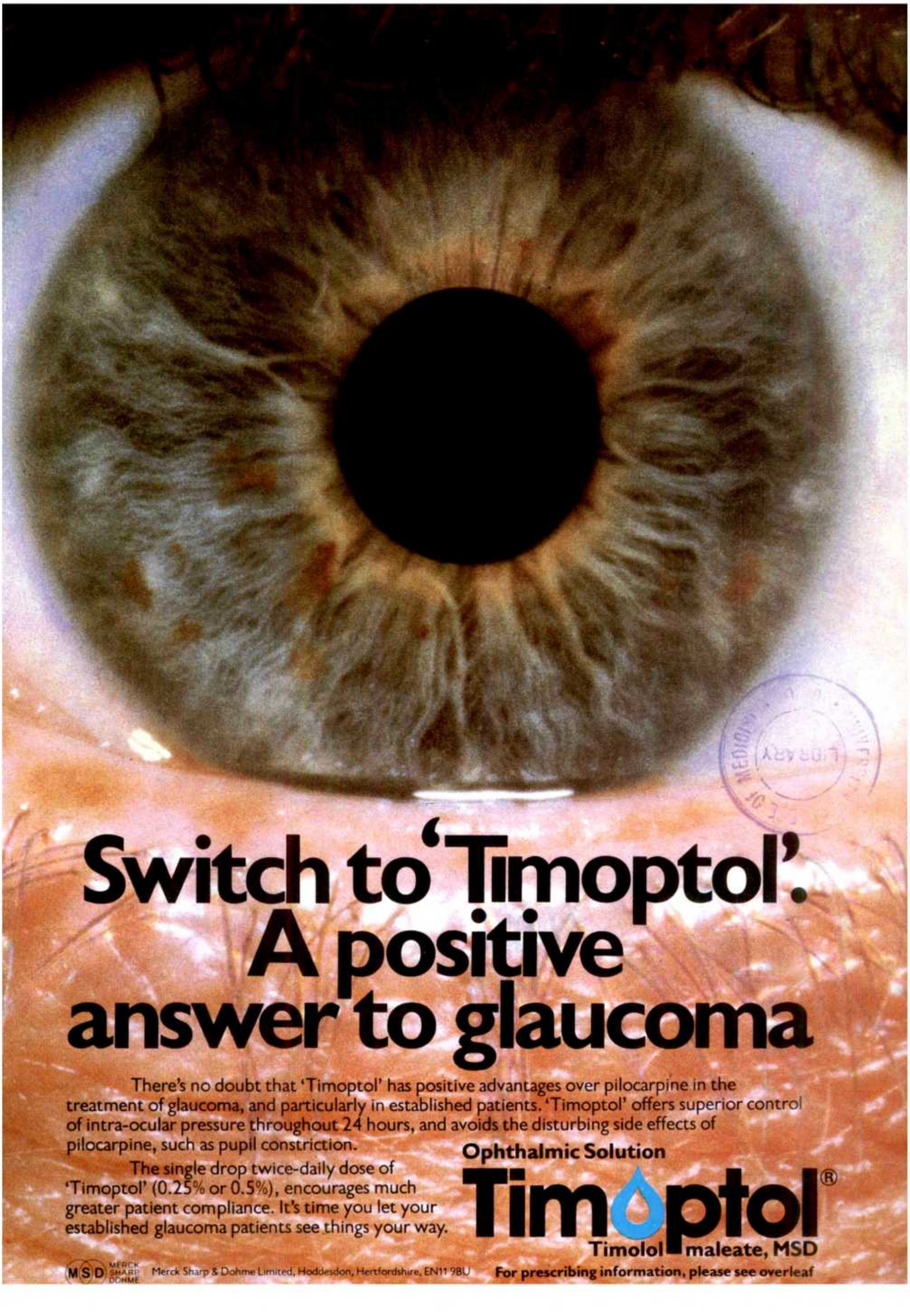

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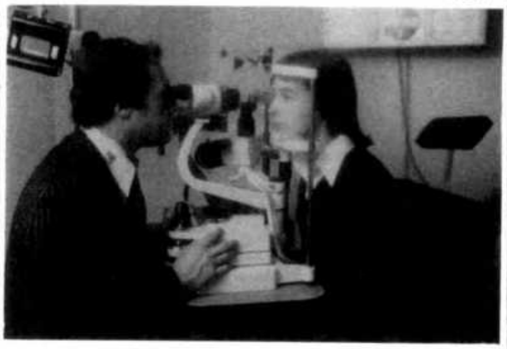

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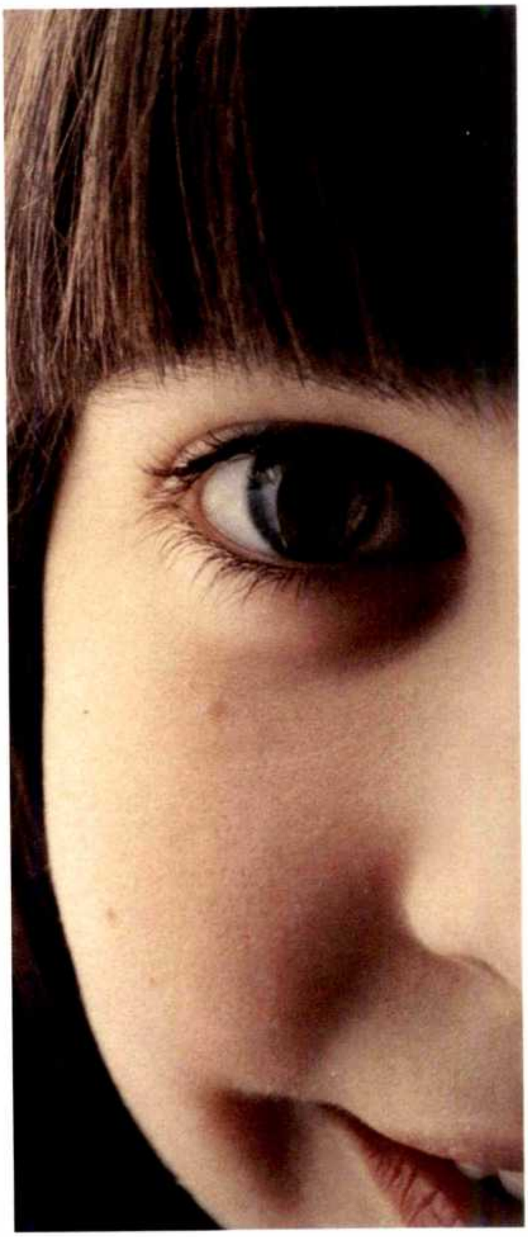

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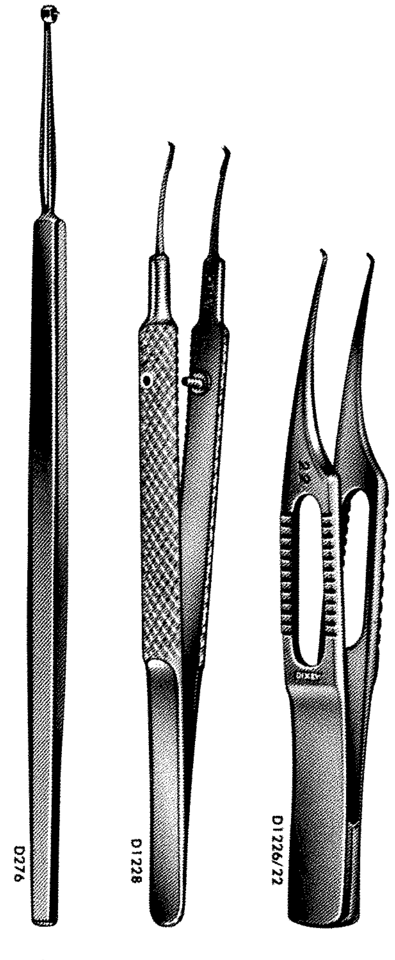

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British Journal of Ophthalmology, 1982, **66**, 417–421

Absence of abnormal erythrocyte superoxide dismutase, copper, or zinc levels in patients with retinitis pigmentosa

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SUMMARY Blood samples obtained from 22 patients with retinitis pigmentosa, 6 unaffected family members, and 8 unrelated controls showed serum copper and zinc to be in the normal range, contrary to the results in earlier reports. Likewise no significant variation of erythrocyte superoxide dismutase (SOD) and catalase levels was found between the 3 groups or when the patients were grouped by sex, age, or genetic distribution. The SOD proteins from controls and retinitis pigmentosa patients had identical mobilities on gel electrophoresis, isoelectric points, and heat stabilities. Our studies do not support the use of copper, zinc, or SOD in the diagnosis or treatment of retinitis pigmentosa.

Several studies have considered the connection between possible abnormalities in serum copper levels and the disease retinitis pigmentosa (RP). Gahlot *et al.*[1] reported that for 15 patients serum copper levels were within a normal range but the plasma ceruloplasmin was decreased. In contrast Rao *et al.*[2] reported an elevated serum copper level in a series of 24 patients with decreased ceruloplasmin levels. Bastek *et al.*[3] also reported elevated copper levels in a family with X-linked RP. These results all imply an abnormal copper metabolism in RP patients. However, Ehlers and Bülow[4] found normal values for both serum copper and plasma ceruloplasmin in a series of 11 RP patients. Marmor *et al.*[5] likewise found no abnormalities in serum copper, serum ceruloplasmin, and urinary copper excretion in 38 patients and 15 family members with recessive, dominant, and X-linked forms of RP.

About 60% of total red cell copper occurs incorporated in the enzyme superoxide dismutase (SOD, EC 1.15.1.1),[6] which contains both copper and zinc. Copper is essential for the activity of the enzyme.[7] Nutritional experiments in animals have confirmed that deficiency in copper can decrease the SOD activity in several tissues.[8–10] In a person with copper deficiency the erythrocyte SOD is reported to be decreased by about 50%.[11] Furthermore, measurements with radioactive copper suggest that erythrocyte SOD obtains its copper from ceruloplasmin, indicating that a decrease in ceruloplasmin might affect SOD activity.[12]

The retina has been shown to contain several SOD isoenzymes, the major one being the same as the erythrocyte Cu-Zn enzyme.[13] SOD is part of the natural defence mechanism against oxygen damage and acts as a scavenger for the toxic superoxide radical.[14] Any decrease in the level of this enzyme could result in the accumulation of the toxic superoxide radical which has been implicated in lipid peroxidation, sulphydryl group oxidation, and DNA damage.

The toxicity of the superoxide radicals can also be produced by their reaction with hydrogen peroxide, generating hydroxyl radicals which are highly reactive and affect most biological materials.[15] The enzyme catalase inhibits this reaction by eliminating hydrogen peroxide. The damaging effects of a decreased SOD level might be overcome by an enhanced catalase content, and so this enzyme is also of interest. In view of the conflicting data on copper levels in RP patients and the biological importance of SOD we have compared the levels of copper, zinc, catalase, and SOD in the blood of RP patients, normal relatives,

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and controls. We have also studied the electrophoretic and heat sensitivity properties of the erythrocyte SOD in an attempt to detect any abnormalities in the enzyme obtained from RP patients.

Materials and methods

Venous blood was drawn from volunteer patients (8 males and 14 females between the ages of 14 and 66), 6 family members, and 8 healthy controls. Informed consent was obtained from each volunteer after the nature of the procedure had been explained. All the patients had been diagnosed as having RP by an ophthalmologist. A family history was taken from each patient. The majority of the patients had no family history of the disease, and these diseases were grouped as simplex. The disease in the remainder of the patients was found to be recessive, X-linked, or dominant. Heparinised blood (1000 units/ml) was used for the haemoglobin, haematocrit, catalase, and SOD assays. Serum was used for the copper and zinc assays. Enzyme and haematocrit measurements were conducted on the same day the bloods were drawn, with control and test samples being processed simultaneously. The haemoglobin, copper, and zinc assays were performed on samples frozen at −70°C for up to one week.

The haematocrit was measured with a Sedinak haemometer. The haemoglobin concentration was determined by Drabkin's reagent[16] (Sigma). Catalase activity was measured colorimetrically with dichromate in acetic acid as described by Sinha.[17] Activity of catalase is expressed as μmol hydrogen peroxide decomposed per min per mg of haemoglobin. The haemoglobin concentration was adjusted to 0·1 g/ml and haemoglobin-free samples were prepared for the SOD assay as described by Winterbourn *et al.*[18] The SOD activity was assayed by inhibition of nitroblue tetrazolium reduction by superoxide radicals generated by the xanthine-xanthine-oxidase system.[19] SOD activity is expressed as units/mg of haemoglobin where one unit (U) of activity is defined as the amount of enzyme activity which inhibits the rate of reduction of nitroblue tetrazolium by 50%. It should be noted that the SOD activity values from different laboratories vary widely. The normal values obtained in this laboratory are in the range of 2·0–3·5 U/mg haemoglobin, which agree with those of Winterbourn *et al.*[18] Copper and zinc were determined by atomic absorption spectrometry.[20] Triplicate measurements were obtained on each sample for all assays.

Data were treated statistically by Student's *t* test.[21] The variability of the data is presented as mean±SEM. Differences at $p<0·05$ were considered significant.

Disc electrophoresis was performed in 7·5% polyacrylamide gels with the system described by Maurer[22] except that stacking gels were not employed. Isoelectric focusing was performed in 7·5% polyacrylamide gels with a final concentration of 5% ampholytes (v/v) in the ranges of pH 3·0–10 and pH 4–6·5 (Pharmacia Fine Chemicals).[23] The potential was maintained at 200 V for 3·5 h. After focusing a blank gel was sliced into sequential 5 mm sections. The sections were incubated overnight in 2 ml water and the pH determined. The gels were stained for SOD activity at 37° for 1 hour as previously reported.[13] Absence of dye uptake indicated reaction of the stain with the enzyme and presence of the enzyme. Duplicate gels were stained for protein with Coomassie brilliant blue according to the method of Weber and Osborn.[24]

Heat sensitivity was determined by heating a haemoglobin-free sample[18] to a specific temperature and removing aliquots at certain time intervals. The aliquots were assayed immediately. The samples from control and RP patients were matched for age and sex.

Results

A comparison of copper, zinc, catalase, and SOD levels between 22 RP patients, 6 unaffected family members, and 8 unrelated controls showed all values to be within normal ranges. No significant differences were observed for any of metals or enzymes tested (Table 1). The haematocrits were determined and also found to be within the normal range of 36 to 52 for all 3 groups. The ages of the RP patients studied varied from 14 to 66, but again when comparisons with controls were made by age and sex no significant differences were found (Fig. 1, Table 2).

Recessive, dominant, and X-linked forms of RP were represented in this study, but the majority of our patients had no family history of the disease (simplex). A similar genetic distribution has been

Table 1 *SOD, catalase, copper, and zinc levels in RP patients, family members, and controls*

	Cu μg/100 ml	*Zn μg/100 ml*	*Catalase**	*SOD U/mg H*
RP patients (n=22)	100±13	104±15	5·9±0·9	2·6±0·7
Family members (n=6)	115±10	102±6	5·1±1·2	3·4±0·8
Controls (n=8)	107±9	108±9	5·8±1·4	3·2±0·7

*μmoles H_2O_2 decomposed per min per mg H.
H=Haemoglobin.
Each value given as the mean ± SEM; for n≥2 the SEM is not applicable.

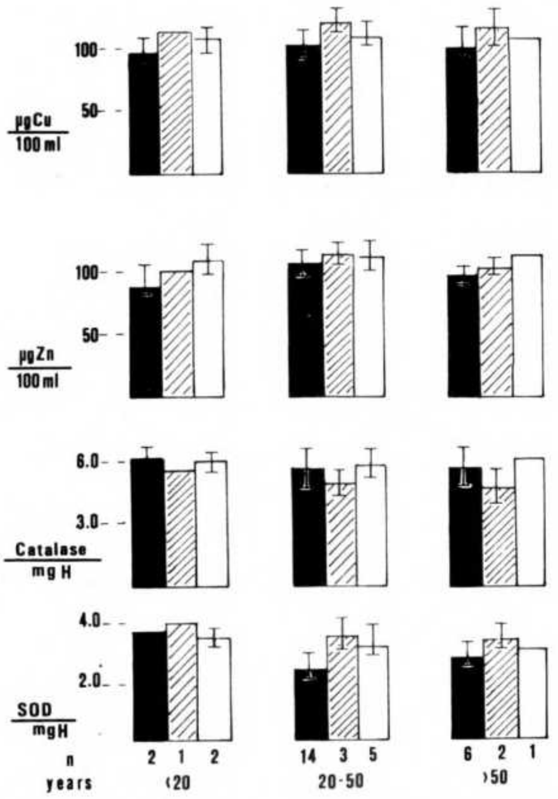

Fig. 1 *Copper, zinc, SOD, and catalase levels compared by age:* ▬ *RP patients;* ▨ *unaffected family members;* ☐ *unrelated controls. Brackets represent SEM; n=number of samples in group; H=haemoglobin.*

Table 2 *Male and female: copper, zinc, SOD, and catalase levels*

Group	*Sex*	*n*	*Cu μg/100 ml*	*Zn μg/100 ml*	*Catalase**	*SOD U/mg H*
RP patients	Male	8	107±15	108±15	6·1±0·4	2·9±0·5
	Female	14	94±13	95±10	5·6±0·8	2·5±0·6
Family members	Male	1	120	110	5·4	3·6
	Female	5	112±8	98±1	5·0±1·0	3·3±0·5
Controls	Male	4	110±10	112±10	5·5±1·0	2·8±0·8
	Female	4	104±7	103±12	6·2±0·9	3·3±0·9

*μmoles H_2O_2 decomposed per min per mg H.
H=Haemoglobin.
Each value is the mean ± SEM; for n≥2 the SEM is not applicable.

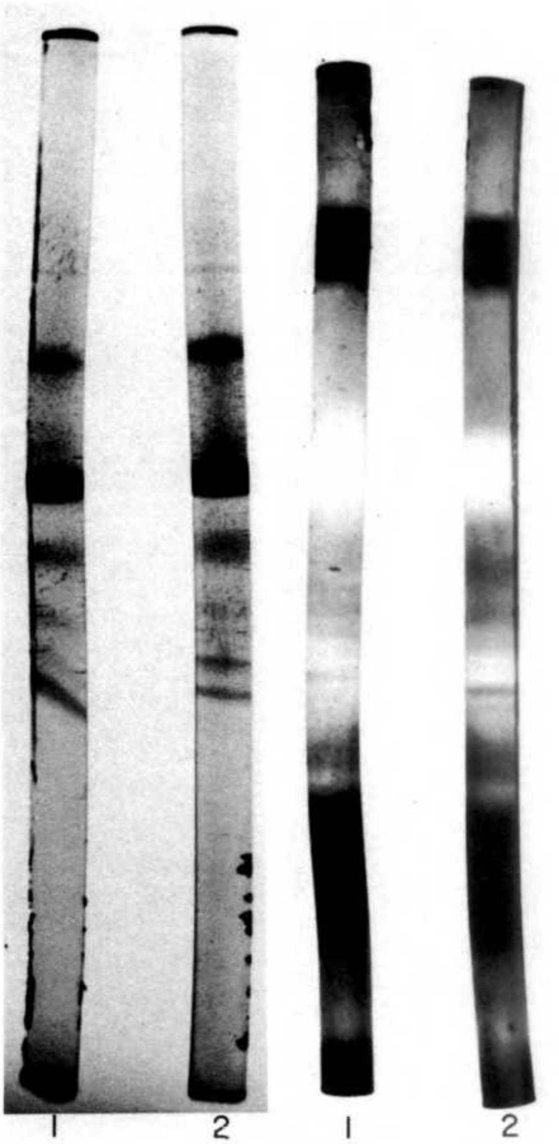

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Fig. 2 *Polyacrylamide gel isoelectrophoric focusing patterns. Normal and RP haemolysates:* (a) *Gels stained for protein: 1—RP; 2—control.* (b) *Gels stained for SOD activity: 1—RP; 2—control; absence of stain indicated SOD activity. The pH range of the ampholytes was 3–10.*

reported by Berson *et al.*[25] From family history the RP patients were grouped as shown in Table 3, and again there was no significant variation of SOD levels.

The erythrocyte SOD enzymes were examined by gel electrophoresis to determine if there were any major differences between controls and RP patients in the enzyme molecular weight or charge distribution. On 7·5% polyacrylamide gels stained for both protein and SOD activity no differences were

Table 3 *Inheritance patterns of copper, zinc, catalase, and SOD levels in retinitis pigmentosa patients*

	n	*Cu* *µg/100 ml*	*Zn* *µg/100 ml*	*Catalase**	*SOD* *U/mg H*
Simplex	12	104±10	106±12	5·7±1·0	2·8±0·5
Recessive	7	98±11	101±5	6·0±0·5	2·9±0·9
Dominant	2	103	98	5·5	2·2
X-linked	1	92	105	5·5	2·6
Female carrier	1	115	104	5·9	3·0

*µmoles H_2O_2 decomposed per min per mg H.
H=Haemoglobin.
Each value is the mean ± SEM; for n≥2 the SEM is not applicable.

observed between control and RP samples. Likewise the isoelectric focusing profiles (Fig. 2) showed the protein with major SOD activity to be identical for both groups with a pI of 4·75, which is identical to that reported for the human SOD.[26]

A comparison of the sensitivity to heat of the SOD enzyme from control and RP patients was made (Fig. 3), and no significant variation in the enzyme stability was observed. At 72°C enzymes from both groups lost about 90% activity in 20 minutes.

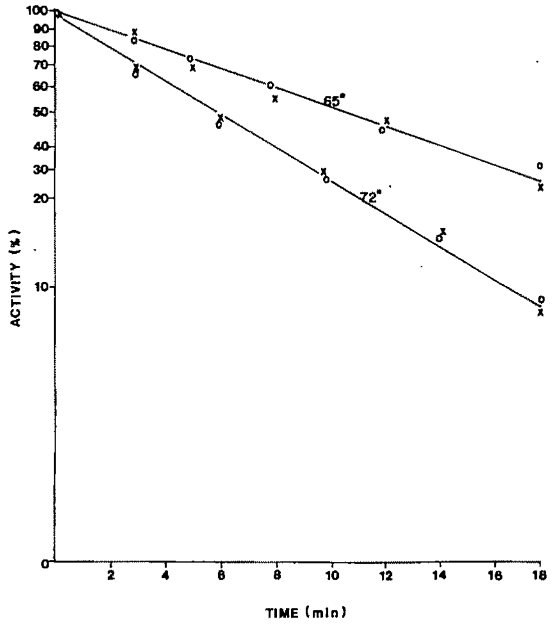

Fig. 3 *Temperature inactivation of enzymes from RP patients and controls. Haemoglobin-free enzyme solutions were subjected to heat at 65°C and 72°C. Aliquots were withdrawn at times indicated and the activities assayed.* O—O *controls;* X—X *RP samples.*

Discussion

Abnormalities in both copper and zinc levels have been reported in patients with RP.[1 2] As the major erythrocyte and retinal SOD enzyme contains both copper and zinc, and as copper deficiency has been linked to a SOD decrease, it seems logical that there might be an abnormal level of this enzyme in RP patients. However, the results of this study did not support these earlier reports of abnormal copper or zinc levels in RP patients. The data were grouped according to age, sex, and inheritance patterns, but no significant variation was detected in any of these classifications. Particular attention was paid to the one case of X-linked RP which we had in the study, but contrary to the report by Bastek *et al.*[2] we did not find elevated copper levels in this patient or the carrier, nor did we find a higher level of zinc in this female carrier. Therefore from our data, and in agreement with the studies of Marmor *et al.*[5] and Ehlers and Bülow,[4] we found no evidence of abnormal copper and zinc metabolism in RP patients, at least in this patient population.

As the copper and zinc levels appear to be normal in RP patients, it is not surprising that we did not detect any abnormalities in SOD levels. Additional evidence that there are no alterations in the SOD enzyme itself is gained from the electrophoretic and heat stability properties of enzymes from control and RP patients. The identical gel patterns of the samples show that the molecular weight and charge distribution are the same for the enzymes. A decrease in the heat stability of several enzymes including SOD[27] with age has been observed. However, in samples taken from controls and RP patients of similar age and sex the sensitivity to heat was the same, and thus there is no premature 'aging' or inactivation of the enzyme. Likewise we observed no major abnormalities in catalase levels. It should be noted that the derivations of the catalase measurements are high and only major differences would be noted. Thus the erythrocyte levels of these enzymes protecting against oxygen toxicity are within the normal range for patients with RP.

The reasons for the discrepancies between our results on copper and zinc levels and those of earlier reports[1 3] remain to be explained and may be due to differences in patient population. However, our studies do not support the use of copper, zinc, or SOD in the diagnosis or treatment of RP.

We thank Dr R. Gadsen, Department of Laboratory Medicine, for the assays of copper and zinc, and Michael Redmond for the isoelectric focusing studies. The help of Dr B. Thompson and Roberta Kimsey in collecting blood and the excellent technical assistance of Gary Kimsey are appreciated. The statistical analysis was performed by Mark E. Lacy. Partial support for this study was provided by the State of South Carolina Appropriation for Research.

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British Journal of Ophthalmology, 1982, **66**, 422–431

Tapetoretinal degeneration in the cerebro-hepato-renal (Zellweger's) syndrome

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SUMMARY Electrophysiological and histopathological study of a baby suffering from Zellweger's syndrome and presenting progressive retinal dysfunction showed this to be related to degenerative changes in the photoreceptor cells and pigment epithelium and to defective myelination of the optic nerve. Disturbances of bile acid and lysine metabolism were also demonstrated, lending support to the concept that Zellweger's syndrome is attributable to a widespread inadequacy of intracellular oxidative function.

The multisystem congenital disorder designated as the cerebro-hepato-renal syndrome[1] was first defined as an entity by Zellweger and colleagues in 1964.[2] Severe dysfunction of the central nervous system is associated with progressive muscular hypotonia and, not infrequently, seizures. Defective liver function is manifested as jaundice and hepatomegaly with, in some cases, hypoprothrombinaemia and gastrointestinal haemorrhage.[3] Clinical evidence of renal involvement in the form of proteinuria is generally minor, though multiple cortical cysts are a characteristic finding at necropsy.[3–5]. A number of other organs, including the thymus and pancreas, the latter manifested as islet cell hyperplasia and hypoglycaemia,[6] may be abnormal, and calcific stippling of the bony epiphyses is common.[7 8] Babies affected by the cerebro-hepato-renal syndrome have a characteristic appearance caused by a high forehead and 'pear shaped' skull, flat supraorbital ridges, micrognathia, high arched palate, and redundancy of the skin of the neck.[3] Malformation of the ears,[3] camptodactyly,[3] and other limb deformities are also well documented. Death within the first few months of life is almost invariable because of progressive cerebral dysfunction, feeding difficulties, and, less often, gastrointestinal haemorrhage.[3]

Ocular disturbance in the cerebro-hepato-renal syndrome is also frequent and can take a variety of forms. The globes may appear unduly prominent as part of the overall facial abnormality, enhanced by puffiness of the eyelids,[3] and nystagmus is a reflection of brain dysfunction. Defects of the globe per se can involve both anterior and posterior segments, presenting variously as corneal clouding, cataract, glaucoma, optic nerve hypoplasia and tapetoretinal dystrophy[1 3 4 9–15] (D. Toussaint, personal communication). However, descriptions of the ocular histopathology are relatively few, and in this report we document the findings in a baby presenting evidence of tapetoretinal dysfunction.

Case history

A female Pakistani baby was born on 2 September 1979, the product of a consanguineous marriage. Birth weight was 2340 g following a normal pregnancy and delivery. On the first day an abnormal facial appearance was observed (Fig. 1) due to a high forehead, epicanthus, and flat supraorbital ridges and bridge of the nose, these latter making the eyes appear to be prominent. Other features included gross hypotonia, jaundice, hepatomegaly, and palpable lobulated kidneys.

The eyes were first examined at 3 weeks of age. Although there was a reaction to light, no following or optokinetic responses could be elicited. Ocular movements were full, with jerk nystagmus on lateral gaze. The eyes were of normal size, with no discernible abnormality of the anterior segments. Pupillary reactions, intraocular pressures, and optic discs were normal, but the retinal arteries were attenuated. A red lesion approximately one-third of the disc diameter in size was seen at the right macula (Fig. 2),

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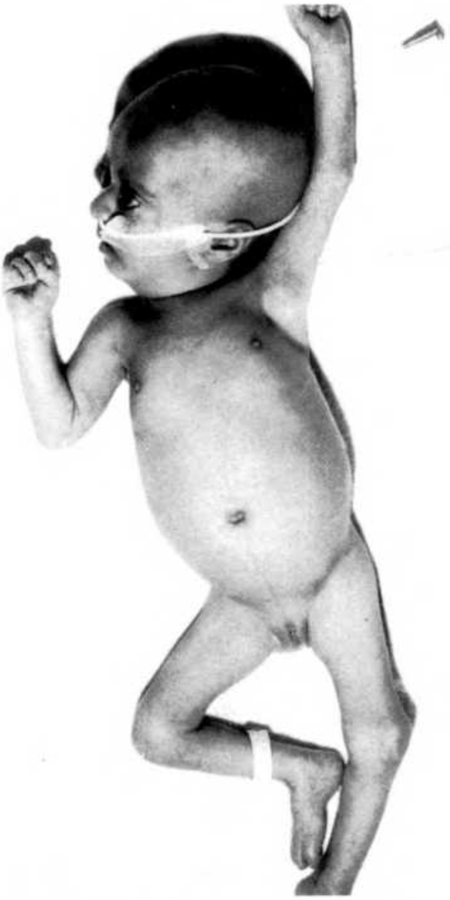

Fig. 1 *Dysmorphic facies with high forehead and prominent eyes due to flat supraorbital ridges.*

while the left macular region contained a central area of deep pigment clumping surrounded by a rim of depigmentation (Fig. 3).

Two siblings, both male, had been born previously. The first born in 1973 is alive and well, but the second born in 1978 died 5 hours postnatally. Post-mortem examination revealed renal cysts. There have been no miscarriages and there is no further relevant family history.

INVESTIGATIONS

Liver function tests were consistently abnormal, including serum bilirubin 140 μmol/l, lactic dehydrogenase 1346 IU/l, serum glutamic-oxaloacetate transferase 546 IU/l, and serum glutamic-pyruvate transferase 187 IU/l. Haemoglobin was 20·6 g/dl, white cells $11\cdot7\times10^{9}$/l, and platelets 150×10^{9}/l. Prothrombin time was normal at 12 s (control 12 s). Urine analysis for bile acids showed the presence of dihydroxycoprostanic and trihydroxycoprostanic acids (46% of 5% respectively of the total) and reduced amounts of their related chenodeoxycholic and cholic acid derivatives (7% and 18% respectively). Liver biopsy showed enlargement of the portal tracts by infiltration with macrophages. Periportal hepatocytes and portal macrophages contained sparse

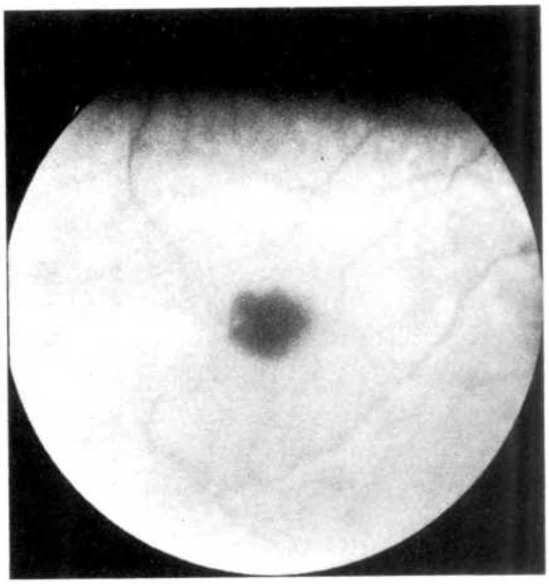

Fig. 2 *Macular region of the right fundus presenting a focal zone of red pigmentation.*

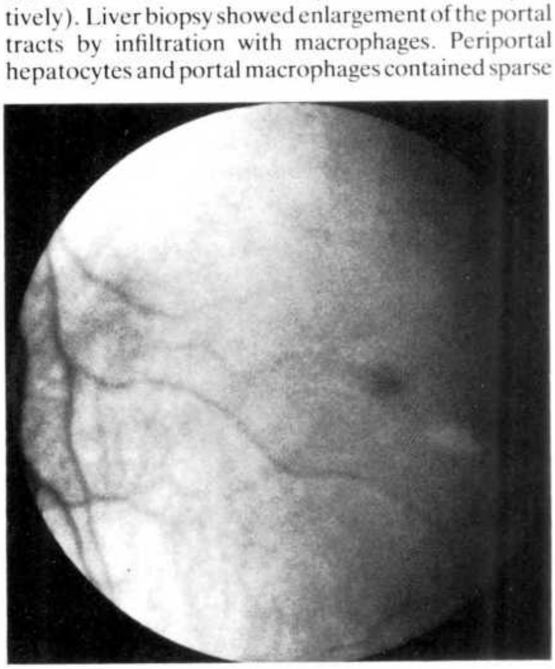

Fig. 3 *Macular region of the left fundus with central area of clumped pigment with a surrounding faint halo of depigmentation.*

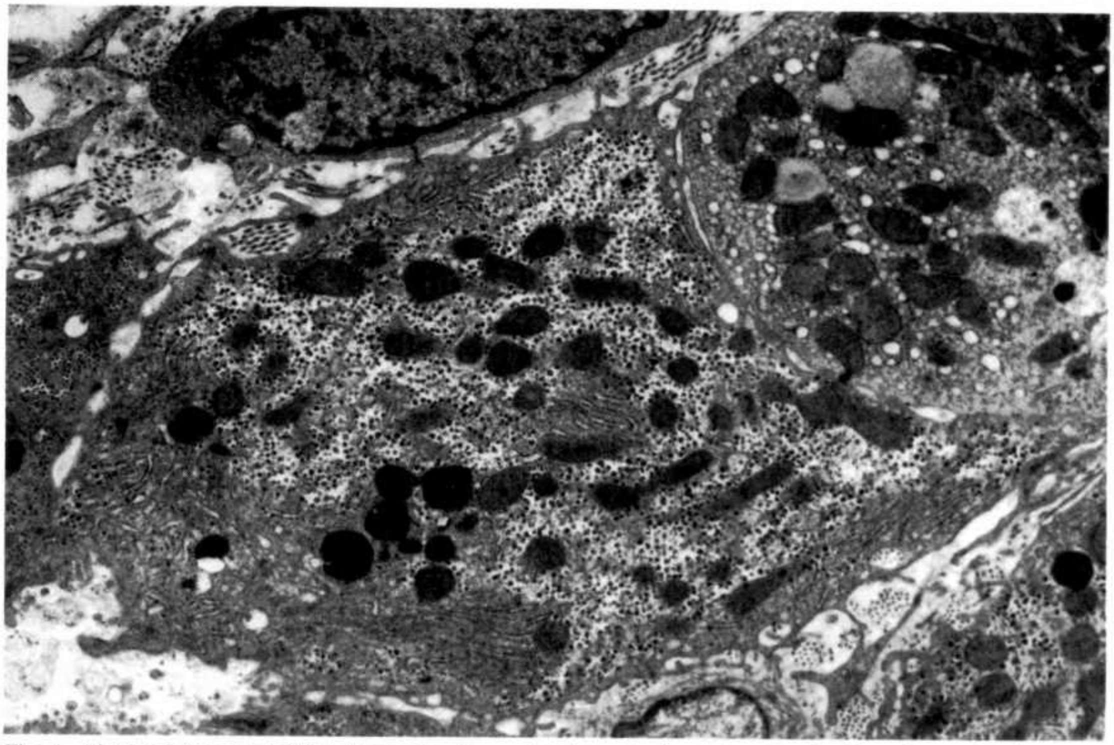

Fig. 4 *Electron micrograph of liver biopsy showing punctate intracytoplasmic iron deposits. Uranyl acetate/lead citrate (×6500).*

pigment granules. Excess iron was observed in hepatocytes and in portal macrophages (Fig. 4).

A pipecolic acid loading test was performed. The 331 ml 24-hour pretest urine specimen contained 24·3 mg pipecolic acid, a substance not normally detectable in urine. Following a 400 mg oral pipecolic acid load the urinary pipecolic acid output increased but the α-aminoadipic acid did not, indicating a metabolic block between pipecolic acid and α-aminoadipic acid.

Ultrasound indicated large cystic kidneys and the intravenous pyelography showed hydronephrosis.

With a noncorneal electrode no electroretinogram (ERG) could be elicited on 3 occasions, whereas with a gold-foil electrode, in contact with the globe, a low-amplitude response was obtained, b wave (a-b peak to peak) 11 μV right and 9 μV left. This ERG was recorded only at 1 month of age, there being no detectable response at 2 months. The wave form of a visual evoked response (VER) to a flash stimulus at 1 month was simple, as compared with that normally seen at this age (Fig. 5). No consistent VER could be elicited one month later. ERG and VER measurements were made with a Medelec MS6 modular electrophysiological system fitted with a DAV6 digital averager.

Over the ensuing 10 weeks the ocular findings, in particular the red lesion at the right macula, remained unchanged. The baby failed to thrive, feeding difficulties and jaundice persisted, and death from bronchopneumonia occurred at 13 weeks of age.

NECROPSY FINDINGS

Macroscopic abnormalities were seen in the liver, kidneys, and brain. The liver weighed 170 g and had a yellow-green appearance, with histological findings comparable to those previously described in the biopsy specimen. Both kidneys were enlarged (combined weight 100 g) and had multiple cortical cysts (Fig. 6), which represented mainly markedly dilated maldeveloped cortical tubules, as a component of a focally dysplastic renal cortex. The surface of the brain contained abnormally small and broad gyri (pachymicrogyria) (Fig. 7). The white matter in the centre of the brain appeared unusually pink. Histological sections of the brain showed, inter alia, islands of neurones remaining between the ependyma and cortex, particularly in the temporal lobes; similar changes of incomplete neuronal migration were present in the external granular layer of the cerebellum. Myelinisation was less developed for the age than normal, and in frozen sections of brain stained

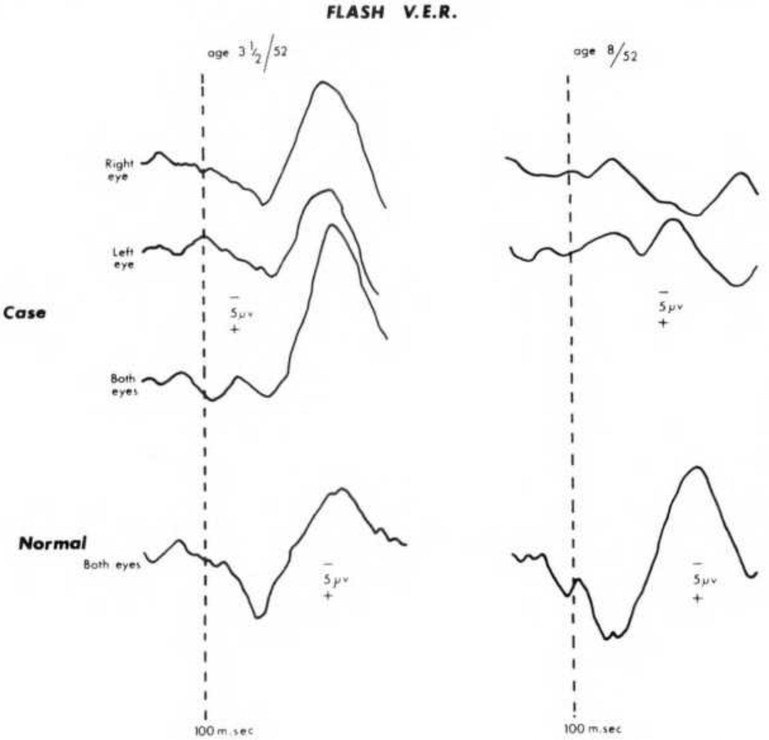

Fig. 5 *Flash VER compared with results obtained from a normal infant (lower traces). Those from the case reported here (denoted by Case in the figure) at 3½ weeks show a recognisable waveform which is not present at 8 weeks, indicating not only failure of normal maturation but also deterioration.*

with oil red O and Sudan black B the commonest cell in the white matter was the swollen astrocyte. In essence the brain changes were those of delayed neuronal maturation, retarded myelination, and lipid-containing astrocytes.

Ocular pathology. Neither eye showed any external abnormality, but owing to a delay of several hours before fixation in formalin both showed some puckering and folding of the retina around the macula.

Light microscopy. There was no apparent abnormality of the corneoscleral envelope in either eye, and the angles of both anterior chambers were normally formed and patent. The lens and ciliary body in both eyes were normal, and the sole finding of note in the anterior segments was generalised lacy vacuolation of the pigment epithelium of the iris. The retinae had suffered considerable autolysis with artefactual detachment, but even in places where separation had not occurred there was unmistakable loss of photoreceptor outer segments affecting chiefly the rods (Fig. 8). Atrophic flattening of the retinal pigment epithelium was widespread, with focal deficiencies and migration of occasional cells away from their attachment to Bruch's membrane (Fig. 9). Small amounts of necrotic debris were also present

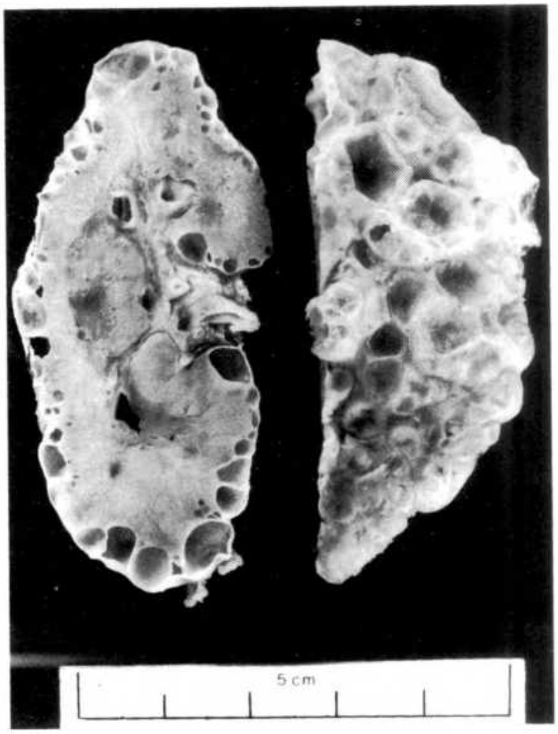

Fig. 6 *Multiple cortical cysts in the bisected kidneys.*

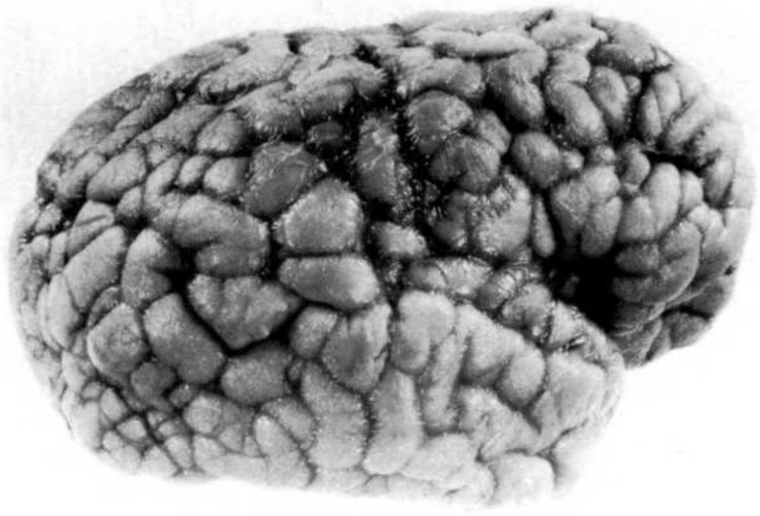

Fig. 7 *The surface of the brain is characterised by both unusually small and large gyri to create a 'cobblestone' appearance. (×0·125.)*

between the degenerate epithelium and photoreceptor cells. The inner layers of the retinae were not noticeably abnormal and showed a conventional organisation. Both optic discs showed an overlying Bergmeister's papilla, while the optic nerve were sites of extensive demyelination and some gliosis.

Electron microscopy. A piece of retina and choroid from the perimacular zone of the right eye was postfixed in buffered glutaraldehyde for transmission electron microscopy. Many of the photoreceptor cells were completely degenerate and were represented by sparse debris, some of it in the form of multilaminated myelin figures (Fig. 10). Others had shed most, if not all, of their outer segment discs, and the inner segments showed considerable loss of mitochondria with exposure of the ciliary roots. Residual mitochondria in these degenerate cells were frequently swollen with ring and other abnormal cristae. No abnormality was recognised in other layers of the neuroretina. The pigment epithelium was flattened and some cells contained somewhat less melanin than normal. A general loss of microvillous processes on the inner surface of the epithelium was observed. Some pigment-containing cells were lying free in the subretinal zone and exceptionally included unusually angulated bodies of moderate electron density presumed to be premelanosomes (Fig. 11).

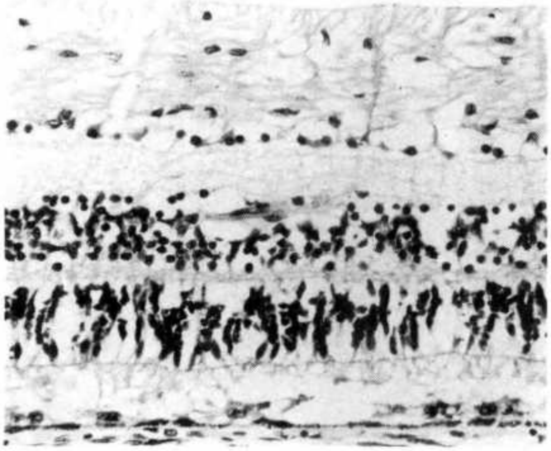

Fig. 8 *The retina close to the optic disc shows an essentially normal organisation, but there is almost total loss of the photoreceptor outer segments and migration of an atrophic pigment epithelium. (Haematoxylin and eosin, ×114.)*

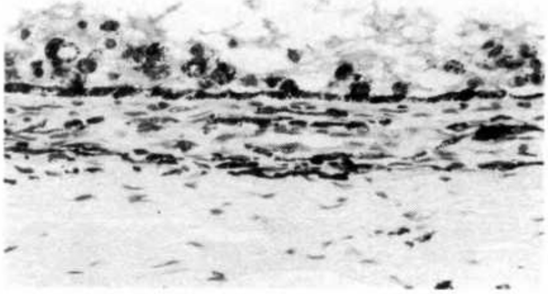

Fig. 9 *The retinal pigment epithelium is flattened and some melanin-containing cells are intermingled with necrotic photoreceptor cell debris in the subretinal space. (Haematoxylin and eosin, ×114.)*

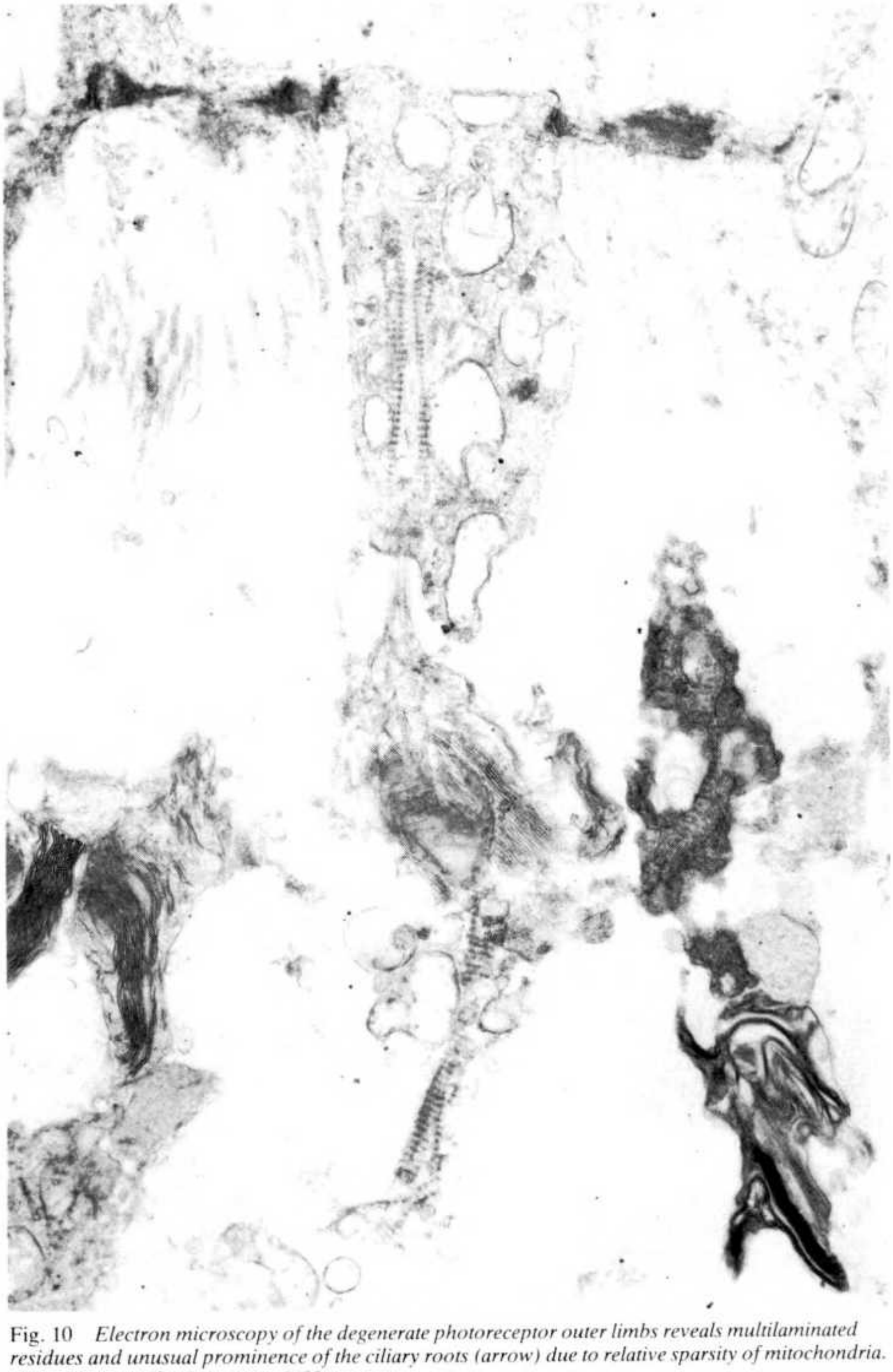

Fig. 10 *Electron microscopy of the degenerate photoreceptor outer limbs reveals multilaminated residues and unusual prominence of the ciliary roots (arrow) due to relative sparsity of mitochondria. (Uranyl acetate/lead citrate, ×6685.)*

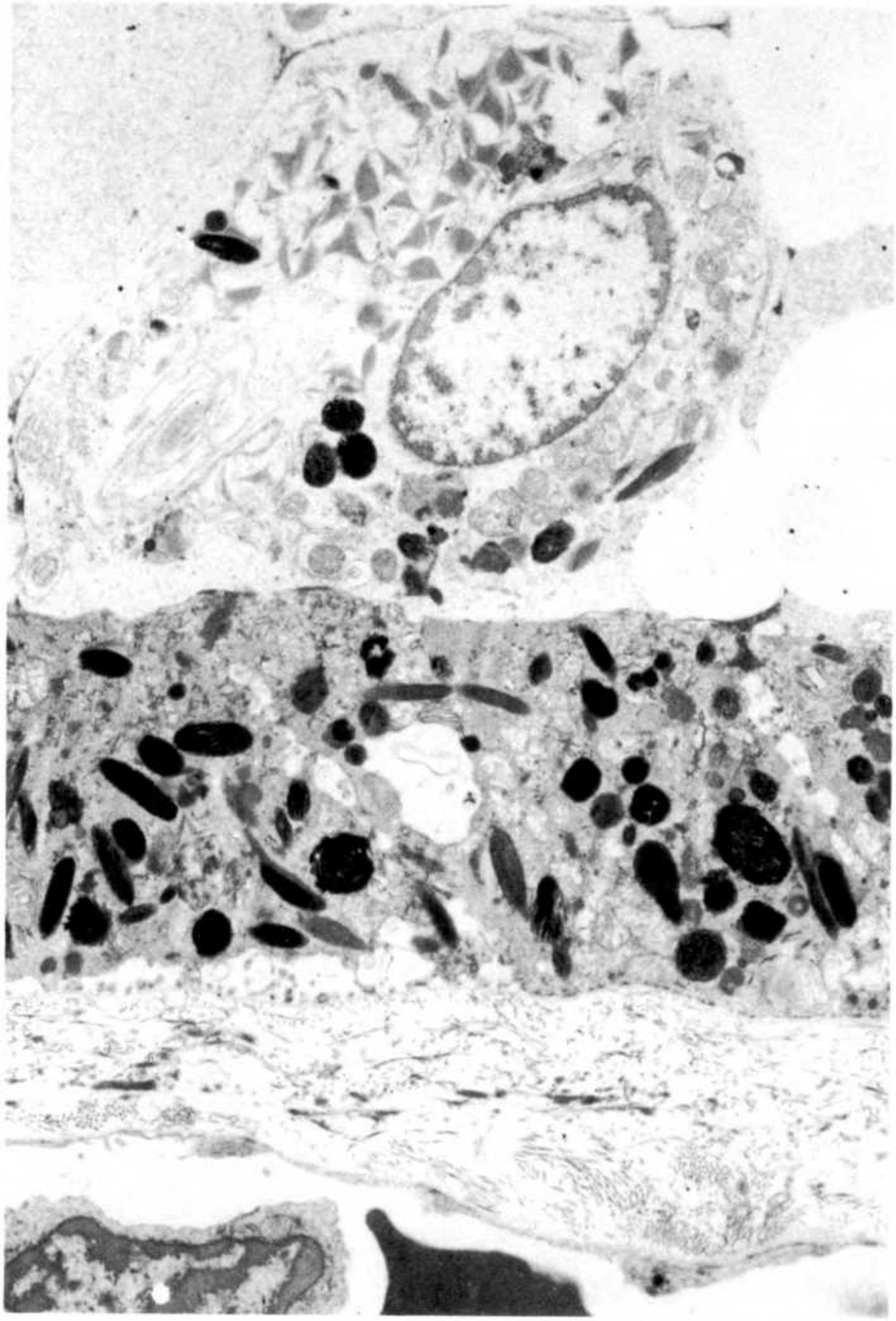

Fig. 11 *The retinal pigment epithelium is flattened with absence of villous processes and incipient detachment from Bruch's membrane. A detached cell on the inner surface of the epithelial monolayer contains several curious angular bodies presumed to be defective and minimally pigmented melanosomes. (Electron micrograph, uranyl acetate/lead citrate, ×6662.)*

Discussion

The combined clinical and pathological findings in our case adequately substantiate the diagnosis of Zellweger's or cerebro-hepato-renal syndrome as defined in the reports establishing the nosological identity of the condition.[1–3]

The most extensively studied changes concern the brain which, to external examination, presents either an excessive number of small gyral infoldings (polymicrogyria)[5,16,17] or a combination of small densely packed and unusually broad gyri (pachymicrogyria).[3,9,10] Histological examination shows changes suggestive of arrested maturation manifested as incomplete migration of cortical neurones and defective myelination of nerve fibres in the white matter with secondary gliosis, which may be associated with the accumulation of sudanophilic material in the phagocytic elements of the central nervous system.[10] The latter have been termed globoid cells, and electron microscopy suggests that they contain multilaminated cytoplasmic bodies.[9,16] Whether the deficiency of myelin and consequent reduction in volume of the white matter is a primary fault in synthesis[17] or, as is perhaps more likely, a destructive process[9,10,16] is unresolved. The dysplasia affects the cerebellum and brain stem structures such as the medullary olives[9,10,16] in addition to the cerebrum.

The hepatic disturbance can assume a variety of forms but according to most reports presents as mild enlargement related to diffuse parenchymal cell damage and intralobular fibrosis.[8] Cholestasis and portal fibrosis characterise some infants[18] and, as in the present case, iron deposition may be found.[3,4,6,8] The origin of the liver disorder is obscure but is possibly secondary to metabolic abnormalities[8,18] rather than to a primary maldevelopment.

Multiple cysts in the renal cortices are an integral part of the syndrome, some representing dilated Bowman's spaces around glomerular remnants[3,8,9,19] with surrounding fibrosis[4,5] and others, as here, being the result of tubular dilatation[5,8] caused by focal dysplasia of the cortex.

Although the character of the involvement may vary, ocular involvement in the cerebro-hepato-renal syndrome is common. Nystagmus features in most cases and is likely to be neurological rather than ocular in origin, particularly as in our case it was observed at only 3 weeks of age and then only on lateral gaze.

Abnormalities of the anterior segment include corneal clouding[3,4,9,11,12,14] which may be associated with raised intraocular tension[11,12] or iridocorneal adhesion and deficiency in the endothelial lining of Descemet's membrane.[14] Bilateral congenital cataracts are not uncommon,[1,3,4,9,14,15,18,20] and, while it does not explain their occurrence, their presence in Zellweger's syndrome with its attendant articular cartilage calcification invites comparison with chondrodystrophia calcificans congenita (Conradi's syndrome), in which lens opacities are usual.[21] Alternatively the concomitance of renal tubular dysfunction, brain abnormalities, and cataracts in both Zellweger's syndrome and Lowe's (oculocerebrorenal) syndrome[22] may be significant. A recent report[15] suggests that heterozygotes also may develop comparable lens opacities. A single report of Brushfield's spots in the iris[3] may be purely coincidental, as may the finding of persistent Bergmeister's papillae in the present case. The pathogenesis of the glaucoma complicating some cases[10–12] is unknown. The vacuolation of the iris pigment we describe has not been commented on in other reports, and, though characteristic of the eye in diabetes mellitus and Hurler-Hunter forms of mucopolysaccharidosis, it can from personal experience sometimes present as a nonspecific finding in many states linked with metabolic dysfunction.

With the knowledge of ocular and visual pathway histopathological findings it is interesting to consider the possible significance of the electrophysiological investigations made at various times during life. The ERG (gold-foil electrode) at one month of age with a b wave amplitude of the order of 10 μV was grossly reduced even allowing for age[23] and below the sensitivity of the noncorneal electrode, thus explaining our failure to demonstrate an ERG using this method. The absence of an ERG one month later could have been due to progression of the pathological process, and it is significant that the ERGs were absent in each of 4 cases examined by Hittner and her colleagues[15] after a minimum of 2 months' survival. The VER at 1 month of age was present but abnormal, and although a large negative wave was always seen at 300 ms the preceding positive wave (200 ms), a prominent component of the normal response, was of reduced amplitude. One month later no consistent VER could be demonstrated clearly confirming that in Zellweger's syndrome degenerative features are superimposed upon a distinct malformation.

The macular regions of the 2 eyes of our case exhibited different features. It would be interesting to know whether the pigmentary disturbance we observed at the left macula was the same as the retinal hole without detachment in the second case reported by Opitz *et al.*[3] The slightly raised red lesion at the right macula was assumed to be a haemorrhage, but, unlike a haemorrhage, no change in its shape or colour occurred over 10 weeks of observation. It should also be noted that in our case there was no bleeding diathesis. Unfortunately due to retinal distortion the macular regions could not be identified histologically.

Posterior segment abnormalities of the kind seen in the present case may be an extension of the anomalous central nervous system development. The first report of sensory disturbance was that of Punnett and Kirkpatrick,[11] the child they documented being unable to follow light at the age of 4 months and presenting a fundus appearance characterised by hypoplasia of the optic disc and pigmentary disturbance. Subsequent authors described attenuation of the retinal vasculature[10 13] and absence of electroretinogram response.[9 13] The first histological description of retinal pathology appears to have been that by Volpe and Adams,[10] wherein they referred to abnormal clumps of pigment epithelium in the peripheral retina associated with reduced numbers of photoreceptor and ganglion cells. Haddad and colleagues[14] described atrophy and gliosis of the optic nerve and retinal nerve fibre layer as well as degeneration of the photoreceptor cells in the macular area. The findings in our own case confirm the outer retinal and optic nerve abnormalities. In retrospect it is surprising that the pupillary reactions were preserved and that there was no dilatation such as is commonly seen in bilateral optic nerve disease. The sequence of events at the tapetoretinal level is obscure, but the relative sparing of the pigment epithelium in a four day old neonate[14] suggests that the primary defect is in the neuroretina. Toussaint (personal communication) undertook a detailed examination of the ocular tissues in an affected baby dying at the age of 7 weeks, and here also the degenerative changes in the photoreceptor outer segments appeared to outweigh the disturbance of the pigment epithelium. The absence of myelin in the optic nerve at the age of 3 months, as pertained in the present case, is abnormal and was probably a reflection of the defective myelination which characterises the brain abnormality in Zellweger's syndrome.

The fundamental fault in the cerebro-hepato-renal syndrome is unknown, but there is increasing evidence of a recessively inherited autosomal gene defect.[3-5 8] It has been suggested that the same defective gene could, by acting at sequential stages in development, be responsible for both the developmental abnormalities and the metabolic disturbances seen in the syndrome.[9 16]

The first metabolic derangement to be described was excessive iron binding by the tissues as demonstrated by electron microscopy in the liver of the present case.[3 24] But this is not a constant finding, and more recently the deposition of iron has been attributed simply to impaired utilisation in association with a failure to thrive and depressed erythropoietic activity.[6 8] So far as the eye is concerned iron has been demonstrated in the epithelium of the cornea and ciliary body (nonpigmented) by Volpe and Adams,[10] but others,[14] including ourselves, have obtained negative results.

Accumulation of pipecolic acid in Zellweger's syndrome, such as was demonstrated in the present case, was first described by Danks and others[8] and since confirmed by Trijbels and colleagues,[25] although a similar disorder presenting a little later in infancy associated with hyperpipecolataemia had already been documented.[26] Pipecolic acid originates from the breakdown of lysine through a subsidiary metabolic pathway and is normally present in the blood in trace amounts only: its role in the symptomatology of Zellweger's syndrome is obscure, although an amine derivative, piperidine, can produce brain damage in mice,[27] and studies in rats indicate that the pipecolic acid pathway is the principal mode of lysine catabolism in the nervous system.[28]

Defective oxidation of bile acid precursors to cholic and chenodeoxycholic acids such that intermediary products are detectable in the serum and urine has also been described.[18 29] The finding of dihydroxy- and trihydroxy-coprostanic acids in the urine of the present case, the former accounting for almost half the urinary bile acid excretion, is in keeping with these reports. It is possible that these and other bile acid precursors are toxic to liver cells and account for the cellular damage in this organ.[18]

To explain the widespread metabolic disturbances in Zellweger's syndrome it has been proposed that there is a generalised disorder of oxidative function caused by defective mitochondrial and peroxisomal activity, Goldfischer and colleagues[30] having earlier described structural and functional anomalies in these organelles. Abnormal morphology of mitochondrial cristae was seen in the retinal photoreceptors in the present case, but it remains to be seen whether such alterations are more than a nonspecific degenerative product.

We thank Dr T. L. Chambers, paediatrician in charge of the patient, for permission to publish this report. Our gratitude is due to Dr D. A. Howell of the Derbyshire Children's Hospital for the neuropathology findings, to Dr Anne Green of the University of Sheffield for the pipecolic acid measurements, and to Dr G. M. Murphy of Guy's Hospital, London, for the urinary bile acid analysis. The technical assistance of Mr R. A. Alexander and Mr R. C. Howes, and secretarial help provided by Mrs P. Goodwin is also acknowledged.

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Factors in the exfoliation syndrome*

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SUMMARY The study cohort consists of 459 subjects over 60 years of age. Intraocular pressure and degrees of exfoliation, lens changes, and pigment were recorded and their interrelationships investigated. A raised intraocular pressure was found to be associated with exfoliation, as also was increased pigmentation and the development of lens changes. An original observation is that the exfoliated males had a significantly higher IOP than their female counterparts.

So-called 'pseudo exfoliation of the lens capsule' continues to arouse great interest because of the uncertainty surrounding the origin of the exfoliated material and its relationship to raised intraocular pressure. The continuing production of the exfoliated material in the absence of the lens[1–3] and the presence of the material outside the eye[4 5] when it could not have got there via the uveoscleral canals[6] confirms a more widespread distribution. Eagle *et al.*[7] found it in the wall of a short posterior ciliary artery in the orbit, and they added further evidence that the material is a form of abnormal basement membrane. This would also explain the reason why the lens epithelium,[8 9] the ciliary epithelium,[2] and the zonule[10] have also been found to produce it. The name of 'the exfoliation syndrome'[11] is therefore more appropriate.

The liberation of pigment into the anterior chamber, with its deposition presumably by gravity in the lower part of the angle, coupled with the depigmentation of the iris and its abnormal vasculature,[12] is also part of the process.

Incidence rates for the syndrome reported to date are predominantly based on males and females combined and ignore possible sex variations. These reports have not been consistent,[13–18] and it is suggested that a large-scale controlled study is required to clarify the issue. It is unusual under the age of 60.

While the existence of its relationship to glaucoma has been known for many years, the mechanism that produces the increase in intraocular pressure has never been clarified, and Pohjola and Horsmanheimo[19] found that the steroid responders in cases with the exfoliation syndrome were no higher than those of the normal population. They postulated that two types of glaucoma processes are involved. The first is a primary simple glaucoma in which both eyes are involved and is steroid responsive. The second type, which is not steroid responsive, is secondary to the exfoliation and affects only one eye.

The frequency of cases of the syndrome in our glaucoma clinics (63%) prompted this investigation. The study was undertaken to elicit its prevalence, relationship with sex, age, intraocular pressure, lens changes, and the type and extent of pigment in the angle.

CLINICAL FEATURES

The syndrome is undetectable except with a slit-lamp or strong loupe. With an undilated pupil dandruff-like deposits are seen at the edge of the iris. When the pupil is dilated the appearance is of a granular peripheral zone and central disc on the superficial layers of the capsule, which present with the classical hoar frost appearance. Between these 2 is a normal-appearing ring of lens capsule which appears to be the area in contact with the moving iris, which supposedly keeps it clear of the deposits.[14] The less usual appearance is that of a peeling of the thin superficial lamella of the capsule in which it becomes rolled, rather like an onion skin. Clumps of exfoliated material are seen in advanced cases on the posterior corneal surface and in the angle. The clumps are also seen on the vitreous face and the pupil edge after cataract extraction.

Increased quantities of pigment cells in the anterior chamber are a constant finding. They derive from the pigment epithelium on the back of the iris, circulate with the aqueous currents, and are washed into the

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*An abstract of this paper was read at the meeting of the Irish Ophthalmological Society, May 1979.

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Table 1 *Indices constructed to measure exfoliation, lens changes, fixed and loose pigment*

Exfoliation *Grade*		*Lens Changes* *Grade*	
0	None	0	None
I	Exfoliation confined to the periphery of the lens and not seen unless the pupil is dilated	I	Slight changes such as vacuoles, spots striae or early nuclear sclerosis
II	Flakes of exfoliated material on the edge of the iris or on the surface of the lens capsule or both	II	Marked clefts or nuclear sclerosis which make only a blurred view of the fundus possible
III	Flakes of exfoliated material in the angle or on the posterior corneal surface	III	Advanced lens changes so marked that no view of the fundus is possible
Fixed Pigment *Grade*		*Loose Pigment* *Grade*	
0	None	0	None
I	Slight browning of the trabecular network	I	Scattering of pigment on Schwalbes line below
II	Definite brown pigmentation of the network	II	Heavier deposits of pigment on Schwalbes line, in the Trabeculum and slightly on the surface of the iris below
III	Heavy infiltration of the network with dark brown or black pigment	III	Heavy clumps of black pigment granules below

trabecular network around the circumference of the angle. On slit-lamp examination the cells can be seen on the corneal endothelium as a Krukenberg spindle and visible as brown particles circulating in the aqueous. The pigment cloud sometimes seen when the pupil is dilated indicates the ease with which these cells are shed. The cells are deposited to a greater degree by gravity in the inferior one-sixth of the angle. Here they can be seen on gonioscopy as heavy black pigment deposits of varying degree on Schwalbe's line and in front of it, in the trabeculum, and on the surface of the iris below; we call these loose pigment. In the rest of the angle the deposits that are found only in the trabeculum into which they are washed by the aqueous are called fixed pigment. Thus while fixed and loose pigment are not exclusive, they represent the circulatory and gravitational deposition of pigment respectively.

HISTOLOGY

Davenger and Pedersen[20] described the histology of the pseudoexfoliated material as consisting of fibrils and a ground substance. The fibrils were of 2 types. Those noted on scanning electron microscopy were coiled in spirals, while those seen on transmission electron microscopy were straight or slightly bent. The main constituent seems to be mucopolysaccharides. The presence of these fibrils was confirmed by Dickson and Ramsay,[21] who described 2 types of differing diameter. Both types were found on the lens, but only the ones of large diameter were found on the iris and ciliary body.

Materials and methods

The subjects examined in the study are in 3 groups, an exfoliated group, a clinic group, and control group aged over 60. The first group was obtained from the outpatient department over a 6-year period because they had the syndrome. The second group was a random sample of clinic patients over 60 years of age. The third group was made up of subjects obtained from 3 geriatric homes, and thus enables the extent of the exfoliation syndrome in the over-60 population to be estimated.

The patients were examined by slit-lamp microscopy, gonioscopy, and applanation tonometry seated upright at the slit-lamp. When no evidence of exfoliated material was seen, the pupils were dilated with cyclopentolate 1% drops, because grade 1 is not visualised until this is done.

The following information was recorded for each subject: (*a*) sex; (*b*) age; (*c*) for each eye (1) pressure, (2) exfoliation, (3) lens changes, (4) fixed pigment, (5) loose pigment.

In quantifying or measuring exfoliation, lens changes, and fixed and loose pigment the observer is faced with the usual problems presented by qualitative information, and every effort was made in the construction of the indices to provide distinct and mutually exclusive categories. Reproducibility tests indicate that the following indices constructed for the present study are reliable (Table 1).

There were 459 study subjects, who were distributed by study groups and sex as listed in Table 2 (average age in brackets).

Table 2 *Distribution of subjects by study group and sex*

Study group	*Sex*		*Total*
	Male	*Female*	
Exfoliation	128 (69·8)	99 (72·9)	227 (71·2)
Clinic	33 (71·2)	71 (76·4)	100 (70·5)
Control	61 (70·7)	67 (70·1)	132 (75·6)
All	222	237	459

Table 3 *Distribution of cases by exfoliation*

Exfoliation	*Frequency*	*%*
None	189	43·6
Unilateral	63	14·5
Bilateral	181	41·9

There was no significant difference in age between the sexes in the study groups.

Results

The subjects were initially classified according to the presence/absence and extent of exfoliation (Table 3).

When we considered the exfoliated cases only, we found that 74% of these were bilaterally exfoliated. The average age of the bilateral cases was 72·1 years compared with 70·1 years for the unilateral cases, but this difference was not statistically significant. There was no significant difference between the proportion of unilateral cases for males and females.

The average pressure of a unilaterally exfoliated eye was 31·4 mmHg compared with 30·5 mmHg for an eye from a bilaterally exfoliated case. Again this difference was not significant. When we considered the average pressure at each level of exfoliation, according to the classification used, for the unilateral and bilateral groups, there was no significant difference at grades I and II, but at grade III the average pressure for unilateral cases was significantly higher ($p<0{\cdot}05$).

The distribution of pigment of the 2 types measured is given in Table 4.

While degree of exfoliation was related to degree of pigmentation in both unilateral and bilateral groups, the pigmentation was generally more advanced in the bilateral cases. Finally, 64% of bilaterally exfoliated eyes had lens changes compared with 51% of the unilateral series (NS).

When the nonexfoliated eyes from the unilateral cases were compared to the eyes from normal cases, a small but significant increase in IOP was found, there

Table 4 *Percentage distribution of pigment for unilateral and bilateral exfoliated cases*

Group	*Fixed pigment*				*Loose pigment*			
	Grade				*Grade*			
	0	*I*	*II*	*III*	*0*	*I*	*II*	*III*
Unilateral	18%	42%	38%	2%	18%	38%	36%	8%
Bilateral	6%	44%	42%	8%	2%	35%	50%	14%

Table 5 *Comparison of nonexfoliated cases with nonexfoliated eyes from the unilateral series*

	Fixed pigment				*Loose pigment*				*Lens changes*				*IOP*
	0	*I*	*II*	*III*	*0*	*I*	*II*	*III*	*0*	*I*	*II*	*III*	*Mean (SEM)*
Eyes from nonexfoliated cases	72%	22%	5%	1%	39%	51%	9%	1%	52%	35%	10%	3%	16·7 (0·21)
Nonexfoliated eyes from unilateral series	36%	42%	16%	6%	22%	53%	22%	3%	57%	32%	7%	4%	18·5 (0·85)

Table 6 *Average IOP level at each grade of exfoliation*

Grade of exfoliation	*Freq. (%)*	*IOP*	
		Mean	*SEM*
0	443 (50%)	17·0	0·22
I	90 (10%)	27·4	1·52
II	287 (32%)	31·6	0·89
III	72 (8%)	30·3	1·94

Table 7 *Frequency distribution of exfoliation by fixed and loose pigment (row percentages in parentheses)*

Grade of exfoliation	*Fixed pigment*					*Loose pigment*			
	0	I	II	III		0	I	II	III
0	250 (68)	89 (24)	24 (7)	5 (1)	0	136 (37)	189 (51)	38 (10)	6 (2)
I	8 (21)	20 (51)	8 (21)	3 (8)	I	3 (8)	18 (46)	17 (44)	1 (3)
II	12 (7)	73 (39)	88 (47)	13 (7)	II	8 (4)	58 (31)	94 (51)	26 (14)
III	4 (8)	27 (52)	18 (35)	3 (6)	III	2 (4)	21 (40)	21 (40)	8 (15)

Table 8 *Percentage distribution of pigment at each level of exfoliation*

Grade of exfoliation	*Fixed pigment*					*Loose pigment*			
	0	I	II	III		0	I	II	III
0	60 (73)	31 (20)	8 (6)	1 (1)	0	34 (38)	50 (52)	15 (8)	1 (2)
I	— (35)	63 (44)	25 (17)	12 (4)	I	— (13)	38 (52)	62 (31)	— (4)
II	4 (9)	43 (35)	46 (50)	7 (6)	II	1 (8)	36 (26)	52 (49)	12 (17)
III	— (12)	47 (55)	47 (27)	5 (6)	III	5 (3)	47 (36)	37 (42)	11 (18)

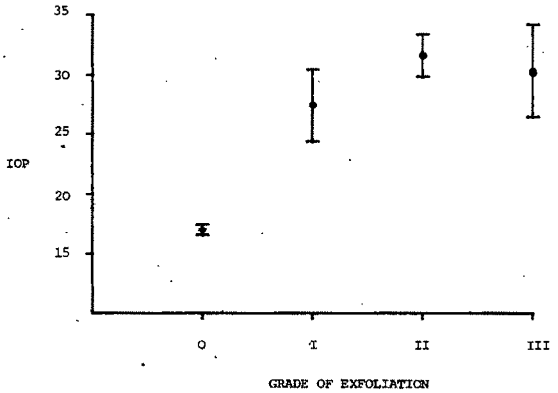

Fig. 1 *Average IOP at each level of exfoliation (mean±2 SEM).*

was greater fixed and loose pigment, while no difference in degree of lens changes was seen (Table 5).

RELATIONSHIPS OF EXFOLIATION

In order to evaluate in more detail the relationships of exfoliation, all eyes in the study were now pooled into 4 groups according to degree of exfoliation, and the average IOP for each level was calculated (Table 6).

The distribution of pigment, both loose and fixed, was next obtained (Table 7).

The association between pigment and exfoliation was highly significant ($p<0.01$) in both cases. This is illustrated by the fact that only 32% of nonexfoliated eyes had fixed pigment of some degree compared with 92% of eyes with grade IV exfoliation. The corresponding figures for loose pigment were 63% and 96% respectively.

Further, the associated fixed pigment was more advanced at each grade of exfoliation for males, while the loose pigment was more advanced for males only at grade II exfoliation (Table 8).

The breakdown of exfoliation by lens changes is as follows (Table 9).

There was a strong relationship in this case also ($p<0.01$), where 47% of nonexfoliated eyes had some lens changes compared with 72% for the exfoliated eyes.

Table 9 *Frequency distribution of degree of lens changes for each grade of exfoliation (row percentages in parentheses)*

Grade of exfoliation	*Lens changes*			
	0 I	*II*	*III*	
0	232 (53)	152 (35)	40 (9)	16 (4)
I	35 (37)	32 (36)	12 (13)	11 (12)
II	108 (38)	9 (32)	48 (17)	39 (14)
III	20 (28)	22 (31)	16 (23)	13 (18)
All	395 (45)	296 (33)	116 (13)	79 (9)

Since the main factors in the study have been shown to be related, it is important to investigate for possible interactions. An analysis of variance was carried out on IOP using degree of exfoliation, pigmentation, lens changes, and sex as explanatory variables. This analysis provided a very interesting and unexpected interaction between exfoliation and sex on IOP (Table 10).

This demonstrates clearly that the increase in IOP with exfoliation was significantly higher for males at every degree of exfoliation (I–III).

Since it is seen from Table 11 that the pressure response to exfoliation is severe generally only in the presence of fixed pigment, and that exfoliated females have less fixed pigment, it is necessary to investigate the effect of fixed pigment on the sex difference shown in Table 9.

However, even when controlled for the degree of fixed pigment, the average IOP was lower for females in most combinations of exfoliation and fixed pigment (Table 12).

The only other significant interaction was that

Table 10 *Average IOP for each grade of exfoliation by sex*

Grade of exfoliation	*Intraocular pressure*					
	Male			*Female*		
	Freq.	*Mean*	*SEM*	*Freq.*	*Mean*	*SEM*
0	189	17·1	0·36	253	16·8	0·28
I	49	30·8	2·27	40	23·3	1·77
II	162	34·2	1·17	125	28·1	1·31
III	31	35·8	3·21	41	26·2	2·25

Table 11 *Average IOP at each grade of exfoliation and fixed pigment*

Grade of exfoliation	Fixed pigment			
	0	I	II	III
0	16	17	20	22
I	17	28	34	—*
II	22	29	34	36
III	13	29	36	—

*Insufficient numbers of eyes to allow estimate.

Table 12 *Average IOP at each grade of exfoliation and fixed pigment (female results in parentheses)*

Grade of exfoliation	Fixed pigment				Number of eyes
	0	I	II	III	
0	16 (17)	18 (17)	19 (21)	23 (21)	149 (318)
I	— (17)	32 (24)	40 (28)	— (—)	16 (22)
II	25 (20)	32 (25)	37 (30)	43 (26)	101 (85)
III	— (13)	36 (25)	35 (36)	— (—)	19 (33)

Table 13 *Average IOP at each grade of exfoliation and lens changes*

Grade of exfoliation	Lens changes			
	0	I	II	III
0	17·2	16·4	16·8	18·4
I	30·4	24·5	30·7	22·5
II	32·4	34·0	29·2	25·5
III	34·9	26·9	29·5	27·1

between exfoliation and lens changes where the presence of severe lens changes seemed to reduce the hypertensive response to exfoliation (Table 13).

In the absence of exfoliation no significant difference in IOP was found with increasing lens changes. This was not the case in exfoliated eyes, where the average IOP for grade III lens changes was significantly lower ($p<0{\cdot}05$) than that for grade 0 lens changes at each level of exfoliation.

In the population group of 132 subjects there were 14 (11%) cases of exfoliation, 75% of whom had raised IOP (>22 mmHg) in the affected eye(s). Seven of these cases had unilateral exfoliation. The common occurrence of minor deposits of loose pigment in elderly people is confirmed in this group, where 65% were affected. Finally, 27% of the clinic group had some degree of exfoliation.

Discussion

The individual and combined effects of the different factors which make up the exfoliation syndrome have been investigated. Their influence on the exfoliation/intraocular pressure relationship were also evaluated, and we found that the degree of pigmentation, extent of the lens changes, and sex were important elements.

We note that 50% of people aged over 60 have grade I loose pigment, and we think that this probably accounts for the conflicting reports on the influence of lower degrees of pigment deposition. Our study shows, however, that once grade II or III loose pigment occurs, the intraocular pressure rises to a pathological level. Previous observers have attributed the increase in intraocular pressure to blockage of the outflow channels by exfoliated material and pigment. Our studies show that the latter is the more important of the two.

A strong association between the development of lens changes and the exfoliative process has been found, but this may be a passive relationship as both are senile conditions. The more interesting finding is that advanced lens changes are associated with a small but significant decrease in the intraocular pressure in exfoliated eyes.

A sex association was of particular interest in that at each level of exfoliation a higher intraocular pressure was found in males. This unexpected result persists even when controlled for degree of fixed pigment (Table 12). Further research is obviously essential to substantiate the sex difference in the IOP response to exfoliation reported in this paper, and to explore the factors responsible for it.

The 74% of bilaterality is higher than average (50%–70%) but may be due to the age criterion in selection. We do, however, note a slight increase in the intraocular pressure in nonexfoliated eyes for the unilateral series, which agrees with Aasved's findings.[15] We also noted that this is accompanied by a significant increase in the deposition of pigment. Thus investigation of nonexfoliated eyes in the unilateral series suggests a stochastic progression of fixed pigment deposition, an increase in the intraocular pressure, and the onset of exfoliation in that order.

To conclude, we emphasise the importance of pigmentation in the relationship between exfoliation and raised intraocular pressure. We point to the high incidence of exfoliation in patients over 60 years old who attend the hospital outpatient departments. We suggest that pigment is deposited initially and that this is followed by an increase in intraocular pressure and then the deposition of the exfoliated material.

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British Journal of Ophthalmology, 1982, **66**, 438–441

Galactose intolerance and the risk of cataract

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SUMMARY Cataracts may arise in association with various major and minor disorders restricting galactose metabolism, and the risk is broadly associated with the degree of galactose intolerance. A family is described in which a girl presented at the age of 7¾ years with cataracts, galactosuria, and partial deficiencies of the enzymes galactokinase and galactose-1-phosphate uridyl transferase. Galactose intolerance as determined by an oral test was impaired and fluctuated with variation in activity of the above galactose enzymes. Minor defects were also present in the parents and a maternal half-brother. The child has a compound disorder of galactose metabolism differing from those previously described. Assessment of galactose tolerance may be useful in the investigation of families with an incidence of cataract.

Various disorders restricting galactose metabolism may be associated with the development of cataract, apparently via osmotically induced damage consequent to galactikol accumulation within the lens.[1] The association with cataract is very strong for homozygous galactokinase deficiency and moderate for heterozygotes, with expression predominantly and perhaps entirely restricted to the first year of life.[2 3] The association is also strong for galactosaemia—homozygous galactose-1-phosphate uridyl-transferase deficiency—and for some rare variant forms associated with considerable reduction in the activity of this enzyme. Heterozygotes for galactosaemia are occasionally detected on screening of patients with cataract,[4] but observations within known affected families suggest that the risk is at most slight. The Duarte/normal heterozygote representing the commonest of the variant forms carries about 75% of the mean normal activity for galactose-1-phosphate uridyl transferase and is not at particular risk of cataract. Minor maternal deficiency or low-normal activity of this transferase or particularly of galactokinase may also be associated with congenital cataracts in an apparently enzymatically normal child,[5] through undefined influences during pregnancy. Deficiencies of other enzymes such as UDP galactose-4-epimerase, which also affect the mainly hepatic conversion of galactose to glucose phosphates, are not alone associated with cataract,[6 7] though combination defects as above are not described.

Within the defined genetic disorders the risk of cataract is broadly correlated with the degree of galactose intolerance. Thus homozygotes for galactokinase deficiency or galactosaemia, and double heterozygotes for galactosaemia and low-activity forms of the transferase such as the Rennes variant,[8] show galactose intolerance and cataracts, as is also found with some cases of heterozygous galactokinase deficiency.[9–11] Heterozygotes for uridyl transferase galactosaemia are not biochemically intolerant.[1 10] Interestingly, double heterozygotes for galactosaemia and the Duarte variant, with about 25% residual transferase activity, may show mild biochemical galactose intolerance,[12–14] as do individuals additionally heterozygous for galactokinase deficiency,[15 16] though cataract or other clinical stigmata may not arise.

Thus an association between galactose intolerance and the risk of cataract is more evident with moderate or severe intolerance. This association is further supported by a study over 3 years of a child with cataracts, trace galactosuria, galactose intolerance, and partial deficiencies of both the above enzymes. She was initially thought to be a double heterozygote for galactokinase and galactose-1-phosphate uridyl transferase deficiency, a combination which has since

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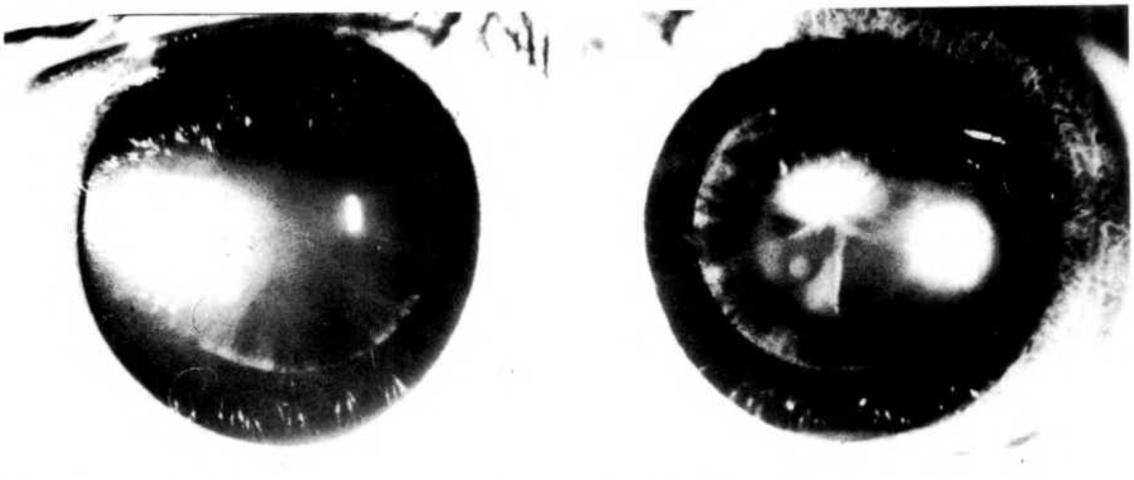

Fig. 1 *Cataracts in a child with galactose intolerance and partial deficiencies of galactokinase and galactose-1-phosphate uridyl transferase. The opacities are lamellar, with nuclear elements, and more evident in the left lens. Left: right eye. Right: left eye.*

been described.[15 16] Of late, however, intolerance to galactose as determined by an oral test has improved in parallel with a reduction in the degree of deficit for both enzymes, and a family study has confirmed that known monogenic disorders are not involved. The child represents a new and possibly acquired syndrome, and the further implications of galactose intolerance in relation to cataract are discussed.

Case report

PRESENTATION AND INITIAL ASSESSMENT

A girl aged 7¾ was referred for assessment of a left intermittent divergent squint: bilateral lamellar cataracts with a nuclear element, left more than right, were then observed (Fig. 1). Routine investigation of juvenile cataract[17] included blood for calcium, protein, and glucose—all normal—and urine for sugars by thin-layer chromatography—galactose identified. Enzyme studies on fresh erythrocytes then followed.[18 19] They indicated borderline deficiency of galactokinase at 1·0 μM galactose consumed/g Hb/hour (normal$>$1·0 unit) and clear deficiency of galactose-1-phosphate uridyl transferase activity at 13·6 μM galactose consumed/g Hb/hour (normal$>$18 units). These deficiencies were confirmed 3 months later with values of 0·9 and 11·6 units, respectively, by an improved method for the transferase.[20] All data cited were derived from consistent triplicate determinations for galactokinase and duplicate or triplicate values for transferase activity.

Galactose tolerance was assessed by a new procedure in which an oral load of 20 g galactose incorporating 200 mg of the nonmetabolised sugar 3-0-Me-glucose is administered in the fasting state (Menzies and Mount, in preparation). Results are expressed as the ratio of galactose to 3-O-Me-glucose present in the urine output over the next 5 hours. Normal adults and juveniles have galactose/3-O-Me-glucose excretion ratios below 6, mean value approximately 2·0. Retarded galactose metabolism (intolerance) increases this ratio, and our patient was clearly intolerant with an excretion ratio of 10·6.

FURTHER ASSESSMENT

The child had been born by lower segment caesarian section at 32 weeks owing to cessation of growth. Her weight at birth was 2 lb 6 oz (1077 g). She had incubator support for some weeks and returned home at 2 months. The mother had a definite rubella contact during early pregnancy. The child was rather small, but general physical examination was otherwise normal. Visual acuity was R 6/12, L 3/60. The fundi were not clearly seen, but there was no evidence of retrolental fibroplasia. There were some behavioural and reading difficulties at school, and the child still preferred assistance with dressing.

It was not established that the cataracts and possibly also the behavioural problems arose in consequence of the galactose intolerance. However, a trial of galactose restriction was undertaken as systemic galactose problems were evident, the cataracts were not extensive and were of uncertain duration, and in view of the clear evidence of regression of early galactose-dependent cataracts on dietary control.[2] Good family compliance was reported. After 12 months the opacities and behavioural problems remained unchanged and the diet was discontinued. Galactose intolerance was confirmed 3 months later, the galactose/3-O-Me-glucose excretion ratio then being 13·8.

FAMILY STUDIES

Our patient is the only child of healthy unrelated English parents. The mother showed normal erythrocyte galactokinase activity and borderline transferase deficiency at 17·5 μM galactose consumed/g Hb/h (normal>18). The father showed normal transferase activity with borderline galactokinase activity at 0·9 μM galactose consumed/g Hb/h (normal>1·0). But neither parent was galactose intolerant, showing galactose/3-O-Me-glucose excretion ratios of 2·1 and 1·33 respectively. A maternal half-brother then aged 18 years showed an excretion ratio of 5·8. Analysis by isoelectrofocusing[21] of the galactose-1-phosphate uridyl transferase activity in fresh haemolysates from the parents and subsequently from the patient indicated that the patterns for heterozygous galactosaemia, Duarte, and other defined variant forms of this enzyme were not present.

PRESENT STATUS

Further investigations were performed at the age of 9¾, 9 months after cessation of the special diet. The erythrocyte galactokinase activity was then 1·8 units—that is, normal—and the transferase activity was 15·5 units, still somewhat below normal. Galactose tolerance had also improved, with an excretion ratio of 7·0. Liver function tests were normal. The cataracts were unchanged. The child had transferred to a school for educationally subnormal children and was making good progress there and at home, possibly showing some real behavioural improvement.

Early ovarian failure may occur in girls with galactosaemia,[22] but this influence was not considered in view of the incomplete nature of the enzyme defects and the absence of major familial effects. The child does not have Fanconi syndrome, which may be associated with galactose intolerance independent of enzyme defects in the galactose to glucose pathway.[23]

Discussion

This patient has shown clearly defined galactose intolerance fluctuating in parallel with partial deficiency of galactokinase and galactose-1-phosphate uridyl transferase activity. It may be reasonably assumed that these 2 phenomena are related, although the causation of the enzyme deficiencies is not clear. Erythrocyte galactokinase activity is normally increased during early life,[24] and heterozygotes for galactokinase deficiency then show activity well within the normal range for adults, further complicating assessment in young children. However, the adult range normally applies beyond about age 5 years, and particularly in view of the increase in activity later recorded, and the family data, our patient cannot be regarded as a heterozygote for galactokinase deficiency. The further electrophoretic analysis and family studies also exclude heterozygous galactose-1-phosphate uridyl transferase deficiency and known low-activity variant forms of this enzyme. However, the presence of other genetic influences is indicated by the marginal enzyme deficiencies in the parents and the acceptable but reduced galactose tolerance in the maternal half-brother. Galactose tolerance is related to liver function, but gross abnormalities were excluded at a late stage. It remains possible that these or other now diminished acquired influences were previously involved.

Our patient has cataracts and galactose intolerance with a previously undescribed pattern of enzyme defect. We cannot now be certain that the cataracts seen are an expression of the established restriction in galactose metabolism: the age of onset is uncertain and other possible influences, notably prematurity, were also evident. The association is, however, very persuasive in view of the known general background outlined above. The form of cataract arising in patients with partial disorders of galactose metabolism is not consistent and does not help in the recognition of galactose-dependent lesions.[16]

Considerable practical difficulties arise in the investigation of the uncommon rather than rare partial enzyme deficiencies affecting galactose metabolism.[25] Such investigation is worthwhile, since any further consequences within affected families can be defined, and expression may be controlled by early dietary treatment. Evaluation of galactose tolerance may be helpful both in the definition of those patterns of enzyme deficiency which carry a risk of tissue damage such as cataract, and as a pertinent empirical screen for this general group of disorders.

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British Journal of Ophthalmology, 1982, **66**, 442–445

Effect of a nonsteroidal gametic factor linked to DNA on senile cataract in man

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SUMMARY In view of the results obtained in animal experiments we have studied clinically the effects of administering partially purified gametic extracts to elderly patients with opacity of the lens. Out of 12 patients treated orally or parenterally 10 have shown, on subjective and objective evaluation, a significant increase in vision, a clearing of the opacity of the lens, and an improvement of general mental and physical conditions.

Many experimental data show that the male gamete contains one or more hydrosoluble nonsteroidal and nonhistone factor(s) of low molecular weight (1000–1500 daltons), probably strongly linked to nuclear chromatin, acting on transcriptional and translational processes in vitro and in vivo. This factor or factors appears to counteract also, temporally and partially, some dysfunctions normally occurring in the later part of mammalian life, the so-called senescence phenomena.[1–3]

The first experimental proof of this activity was reported by Fachini and Gianfranceschi senior in 1964.[4] These authors achieved evident clearing of the opaque lens in the senile cataract of old dogs by administering parenterally either whole homologous semen or extracts of homologous and heterologous spermatozoa.

Senile cataract is in fact probably one of the more frequent structurally irreversible changes occurring in senescence, and it is a syndrome that, unlike other senile phenomena, may be evaluated almost semi-quantitatively. Further data on the same activity were reported by Maselli *et al.*[5] in 1972 and recently by Lugaro *et al.*[1] in a more extensive research carried out on 43 dogs. At the same time Casellato *et al.*[2] have shown that the same active extracts can normalise in senescent rats the inducibility of some liver enzymes (NADPH-oxidase, tyrosine amino transferase, δ-aminolaevulinic acid synthetase, and also glucokinase), which activity appears to be inversely proportional to the age of the animal. As regards this aspect, Lugaro *et al.*[3] have reported that the activity on the enzyme inducibility may be correlated in the aging animal with a significant increase in the rate of liver transcriptional and translational processes.

In view the results we obtained in dogs we decided to investigate this problem in human cataract by giving partially purified gametic extracts by mouth or parenterally.

Material and methods

Bovine spermatozoa were obtained, as described below, from total semen containing about 10^9 cells/ml.

Extraction and purification of the gametic factor for parenteral use. The whole process of extraction and purification of the gametic factor was done as previously reported.[1] We started not from a gamete homogenate in toto but from dried and lipid-free spermatozoa, isolated from bovine semen according to Borenfreund *et al.*[6] with minor modifications.

The purified extract was ultrafiltered and passed again through a sterilising membrane (porosity 0·23 μm, Millipore), then lyophilised in the presence of glycine as substrate. The samples were sterile, protein-free, and pyrogen-free.

Extraction of the gametic factor for oral use. Dried and lipid-free spermatozoa isolated as described above were accurately homogenised with corindone in saline (50 mM sodium chloride), and the suspen-

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Table 1 *Summary of the results obtained in 6 subjects after 21-day oral treatment (see text). First examination, at the end of treatment; second examination, 30–40 days later. In brackets are indicated the optical corrections employed to obtain these values of visual acuity*

Patient no.	*Sex*	*Age (years)*	*Eye*	*Fundus*	*Lens opacities*	*Vision*		
						Before treatment	*1st examination*	*2nd examination*
1	F	80	R	Miopic choroidosis	Corticonuclear	Counting fingers	Counting fingers	1/50 (−20)
			L		Cortical	3/50 (−20)	1/10 (−22)	2/10 (−22)
2	M	82	R	Vascular sclerosis	Cortical and posterior subcapsular	1/20 (−5)	2/10 (−4)	2/10 (−3)
			L			1/20 (−5)	1/20 (−5)	1/20 (−5)
3	F	85	R	Diabetic retinopatia	Cortical and nuclear	1/50 (−1·5)	1/50	
			L			1/10 (−1·5)	1/10	
4	M	85	R	Papillaris cupping	Cortical, nuclear, and subcapsular	3/10 (−7)	3/10 (−7)	5/10 (−7)
			L			4/10 (−5·5)	5/10 (−5·5)	5/10 (−5)
5	F	88	R	Vascular sclerosis	Cortical and subcapsular	5/10 (+1)	5/10 (+1)	7/10 (+0·5)
			L			1/20 (+1)	1/20 (+1)	4/10 (−0·5)
6	M	75	R	Vascular sclerosis	Coronary and cortical	4/10 (−1)	6/10 (+0·75)	8/10 (+1·5)
			L			Counting fingers	3/50	3/50 (+1·5)

sion centrifuged at 5000 *g* for 30 min. To one volume of supernatant was added one volume of 0·4 M ammonium acetate-ammonia buffer pH 9·5. After precipitation overnight in the cold with two volumes of 95% ethanol, and subsequent centrifugation at 13 000 *g* for 30 min, the supernatant was evaporated to a small volume under vacuum at 30°–35° C. The concentrated solution, brought to pH 9·5 with dilute ammonia, was ultrafiltered through a membrane with a porosity less than 5 nm (Sartorius Membranfilter 12136, mol. wt. cut off 10 000 daltons) and then lyophilised twice. A third lyophilisation was conducted after mixing with an inert compound (glycine).

Steroid content. The presence of free steroids or their conjugates in the extracts was excluded (before and after enzymatic digestion with glucuronidase and sulphatase) by radioimmunoassay for testosterone, 5α-dihydrotestosterone, progesterone, and 17β-estradiol (<5 pg for fraction equivalent to about 10^9 spermatozoa or 1 ml of total semen.)

Treatment. The clinical assay was carried out in 16 elderly patients, all proposed for surgical operation, between 74 and 88 years old, suffering from mono- or bilateral senile cataract. Six patients were treated by mouth, 6 parenterally, and 4 with a placebo (glycine). In the case of oral administration the treatment lasted for 21 days with a quantity of the extract equivalent to about 10^{10} spermatozoa daily. In the case of parenteral administration, two intramuscular injections with a 12-h interval, each equivalent to the extract of $2{\cdot}5 \times 10^8$ spermatozoa/kg body weight, were given.

Orally treated subjects were submitted to a careful inspection of the eyes before the treatment, at the end (1st control), and 30–40 days later (2nd control). Subjects parenterally treated were examined before, 2–6 days after treatment (1st control), and 2–3 weeks later (2nd control).

The examination of the vision and refractory status with the pupil in normal condition, and on biomicro-

Table 2 *Summary of the results obtained in 6 subjects after parenteral treatment (see text). First examination, 2–6 days after treatment; second examination, 2–3 weeks later. In brackets are indicated the optical corrections employed to obtain these values of visual acuity*

Patient no.	*Sex*	*Age (years)*	*Eye*	*Fundus*	*Lens opacities*	*Vision*		
						Before treatment	*1st examination*	*2nd examination*
1p	M	75	R	Normal	Posterior subcapsular	1/10	2/10	
			L	Miopic choroidosis		Amblyopia	Amblyopia	
2p	F	76	R	Normal	Cortical and subcapsular	1/10	2/10	1/10
			L			1/10	2/10	1/10
3p	F	80	R	Normal	Cortical	2/10	3/10	3/10
			L			2/10	3/10	3/10
4p	M	83	R	Vascular sclerosis	Cortical and subcapsular	1/20	1/10	3/10
			L					
5p	F	74	R	Normal	Anterior and posterior cortical	3/10 (−3)	4/10 (−3)	
			L					
6p	F	74	R	Normal	Cortical	6/10 (+1·5)	6/10	
			L			1/10 (+1·5)	1/10	

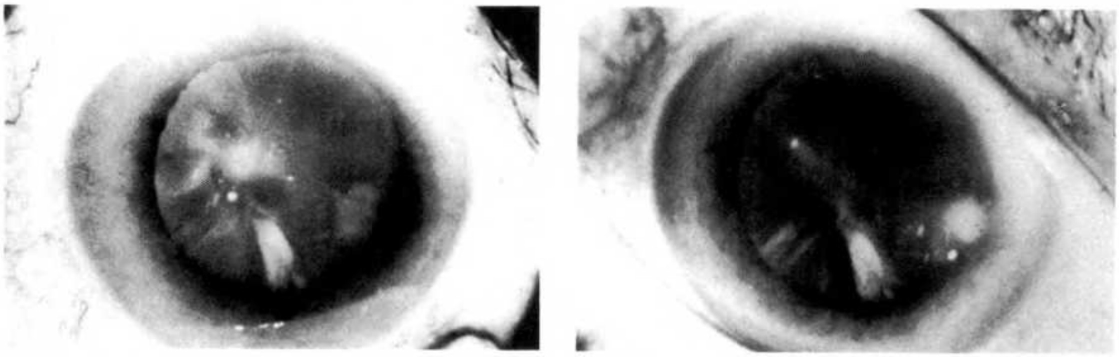

Fig. 1A Fig. 1B

Fig. 1 *Photobiomicroscopy of the crystalline lens of the left eye opacified from senile cataract in patient 5 (see Table 1), before (A, vision 1/20) and after (B, vision 4/10) oral treatment (second examination).*

scopic inspection of the lens under mydriasis, was carried out with a slit-lamp and an ophthalmoscope.

Results

Tables 1 and 2 show the results in treated patients. In the 6 treated by mouth the data (Table 1) show a variable increase in visual acuity, which is shown also by the objective evaluation of the lens. Patients 5 (Fig. 1) and 6 showed the best subjective and objective improvement. In patient 1 (Fig. 2) the increase in vision was satisfactory, as was the related clearing of the lens, particularly in the left eye. Patients 2 and 4 had less improvement, but it was significant. Patient 3 did not come back for the second examination, so any evaluation was impossible.

The vision of the 4 placebo-treated patients was unaltered.

As to the 6 parenterally treated subjects (Table 2), we observed evident improvement of the right eye vision in patient 4p. A slight increase in vision was observed also in patients 1p, 2p, and 3p, although in 2p the increase seemed to be transient; in fact it was no more appreciable at the second examination than earlier. Patients 5p and 6p did not come back for the second examination; patient 6p did not show any variation at the first examination.

Discussion

These findings show that the gametic factor can induce, at least in some subjects, an evident clearing of the initial opacities, chiefly in the cortical layer of the lens. The biomicroscopic observations show a lessening in the typical milky aspect of the lens and a break of the less thick opacities in the cortical layer.

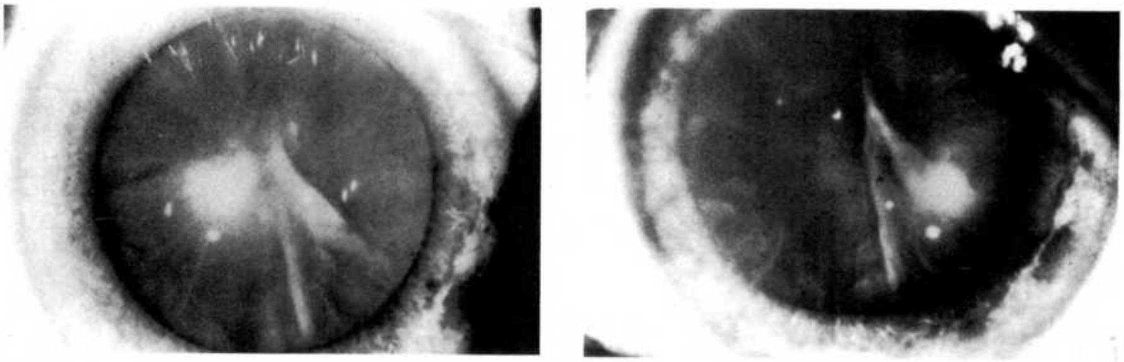

Fig. 2A Fig. 2B

Fig. 2 *Photobiomicroscopy of the crystalline lens of the left eye opacified from senile cataract in patient 1 (see Table 1), before (A, vision 3/50) and after (B, vision 2/10) oral treatment (second examination).*

It would seem, then, that cortical cataract may yield the best results from treatment, while nuclear or posterior subcapsular opacities generally show a minor clearing. In the latter case the partial improvement of vision can be referred only to the clearing of the cortical opacities.

At the same time it is possible to see an objective and a subjective improvement in general health conditions (wellbeing, muscular tone, mental alertness, etc). Among these 'side effects' of the therapy, it is interesting to underline the lessening, in number and intensity, of the so-called maculae cutaneae senilis, the brownish cutaneous spots which occur typically on the back of the hands in old people. As noted previously,[1] we do not know the mechanism of this temporary correction. The results seem to reflect, in the individual and in the organs, what has already been widely observed in haematological, biochemical, cellular, and subcellular variables.[7]

The active factor, which may be a peptide[1] or a family of peptides of low molecular weight naturally linked to nuclear chromatin, exerts an inhibitory action when it is, conversely, in accelerated cytokinetic or cytodynamic conditions (for instance, in a young growing organism). This was shown in trials carried out on the δ-aminolaevulinic acid synthetase inducibility in prepuberal rats,[3] where, in contrast to what takes place in aging rats, the inducibility is significantly decreased owing to a direct action in the transcriptional and translational processes.

This fact leads us to suggest that the considered factor(s) would act as general factor of homoeostasis in more complex mechanisms which control the basal processes of gene expression.[8]

This work was supported by the Programma Finalizzato Biologia della Riproduzione (CNR, Italy).

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British Journal of Ophthalmology, 1982, **66**, 446–449

Visual outcome and effect of treatment in stage III developing retrolental fibroplasia

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SUMMARY Forty-five babies were seen with retrolental fibroplasia (RLF) stage III or more, that is, with a large vasoformative ridge protruding into the vitreous cavity. Thirty-four attended for follow-up, but subsequently 6 died. Of the remainder 12 had satisfactory vision, 3 unilateral and 8 bilateral high myopia, 3 were totally blind, and 2 were partially blind. It was found that stage III RLF could be subdivided according to its severity. Early stage III had a good prognosis, with 11 out of 18 achieving satisfactory vision, but only one out of 16 in RLF stage IIIa or more. Cryothermy was applied to 9 babies in the latter group, but it did not seem to influence the final outcome.

The acute or developing stages of retrolental fibroplasia (RLF) are followed by the stages of resolution and scarring, and it is well recognised that many cases of developing RLF resolve without causing any obvious ocular damage. However, if there is a large ridge of vasoformative tissue occupying one or more quadrants of the globe (stage III, Table 1), then the condition is likely to progress to some degree of permanent retinal damage. There have been several reports[1–7] on the use of laser coagulation, light coagulation, and cryopexy[4] in order to try to arrest the progress of the disease, but the value of treatment is still not fully established. In this paper we discuss 45 cases of stage III RLF, 9 of which received treatment with cryothermy.

Material and methods

During a study[8] on the incidence of RLF in 683 premature babies seen at the Royal Women's Hospital, Royal Children's Hospital, and Mercy Maternity Hospital, Melbourne, in the years 1977–9 developing RLF was found in 41, and a further 2 were seen in the cicatricial stage. In 18 babies the condition did not reach beyond stage II, and in all these the retinal changes seemed to regress completely. However, the remaining 23 did reach stage III or more, and a significant number progressed to permanent retinal damage. These 23 plus the 2 babies seen in the cicatricial stage, and 20 more who were seen with stage III RLF after the end of the survey, are the subjects of this report.

The retinal changes in the developing stages were classified according to the scheme shown in Table 1, while the cicatricial changes are graded according to the scheme in Table 2.[9] At the outset of the survey it was considered that cryothermy should be given to any baby who reached stage IIIa, IIIb, or IV. Ten babies fell into this category, but one was too sick for

Table 1 *RLF stages of development*

Stage I	Temporal vessels terminate in many parallel running finger-like branches Abrupt margin between vascularised and nonvascularised retina temporally
Stage II	Margin between vascularised and nonvascularised retina becomes slightly elevated to form a shelf or shunt in which the branching temporal vessels terminate The peripheral vessels are dilated and often run parallel to the shelf
Stage III	Shelf larger, projecting into vitreous, extending through one or two quadrants. Vascular channel visible in shelf. Moderate dilatation and tortuosity of peripheral vessels
Stage IIIa	Sinusoids visible on surface of shunt. New blood vessels grow into vitreous. Increased generalised vascular engorgement. Shelf extends round 360°
Stage IIIb	Vessels at posterior pole become very engorged and tortuous. Retina oedema. Haemorrhages. Marked vessel outgrowth into vitreous
Stage IV	The shelf becomes larger protruding markedly into the vitreous. The dilatation of the vessels of the posterior pole may become extreme and they seem to arch into vitreous to reach the apex of the shelf. Localised retinal detachment may occur
Stage V	Total retinal detachment from disc to shelf or to ora serrata

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Table 2 *RLF grades of resolution and scarring*

Grade 0	Normal
Grade 1	Mild peripheral changes
Grade 2	Slight dragging of temporal vessels. Heterotopia of macula. Preretinal fibrosis. Myopia
Grade 3	Dragged disc with fibrous tissue in temporal periphery
Grade 4	Retinal fold with fibrous tissue on posterior surface of lens
Grade 5	Peripheral ring-shaped retinal detachment
Grade 6	Total funnel-shaped retinal detachment

Table 3 *Visual status of 45 children who reached stage III developing RLF. Follow-up 8 months to 4 years*

Visual status	*No.*
Satisfactory	15
High myopia	8
Blind	5
Dead	6
No follow up	11
Total	45

treatment, so only 9 were actually treated, 6 bilaterally and 3 unilaterally. Cryothermy was not offered to any of the 20 babies born after 1979, because of the doubtful benefit of the treatment. The procedure for cryothermy was as follows. The Keeler-Amoils cryothermy machine was set at −70° C, and multiple applications were made through the conjunctiva after a surface or local anaesthetic had been applied; general anaesthesia was not required. Treatment was directed to the vasoformative ridge itself, and not the avascular retina in front of it or the neovascularisation behind it. Most children received a single freeze-thaw cycle, but some received a double cycle. The probe was applied until the overlying retina was seen to be frozen.

The methods of examination in the premature nursery involved dilatation of the pupils with cyclopentolate 0·25% and phenylephrine 2·5% eyedrops, and the use of a premature infant speculum to separate the eyelids. The fundus was inspected with a binocular indirect ophthalmoscope and a +30·0 DS lens, while the ora serrata was viewed with a custom-made scleral indenter. Follow-up examinations after the age of 6 months included checking the visual performance and assessing the ocular posture and mobility, refraction, and fundus examination after instilling cyclopentolate 1% drops. However, scleral indentation was not usually performed after one year of age.

Results

The visual outcome of 45 babies seen with stage III RLF is shown in Table 3. In 15 the visual status was classified as satisfactory, as the visual performance was normal for the age, and refraction showed no significant error. High myopia, more than −9·0 DS, was found in 8 cases, and in several it increased rapidly over the first few years of observation. Five children were classified as blind, in 3 of whom the retinae were detached, and there was virtually no perception of light, while in 2 the visual acuity was less than 3/60, and retinae were severely dragged. Eleven children were lost to follow-up, and 6 died.

Children in the treated group fared considerably worse than in the untreated or unselected groups. However, all of these were in RLF stage IIIa or more, and when they were compared with untreated patients of comparable severity (Table 4) there was little obvious difference between the 2. Out of 9 children treated 8 survived, 2 are blind, 4 have high myopia, one unilateral high myopia, and only one is satisfactory, while of the 7 untreated children of comparable severity, 4 survived, 2 are blind, one has high myopia, and one has unilateral high myopia. Of the 18 children with early stage III RLF 16 survived, only one is blind, 3 have high myopia, one has unilateral high myopia, and 11 are satisfactory.

In Table 5 is shown a more detailed analysis of the ocular status in 33 children—the 28 who were followed up plus 5 of the children who died. It can be seen that only 14 eyes are normal (grade 0) out of a total of 66. There are very minor peripheral changes in 11 eyes (grade 1), but even these may be predisposed to a retinal detachment in later life. Twenty-three have a certain amount of vessel drag, and some have severe myopia (grade 2). Eyes in grades 3 to 4 have poor vision, while those in 5 or 6 have very little vision, and 18 eyes came into these 4 categories.

The gestational age and birth weight of the children

Table 4 *Visual outcome of stage III RLF compared with that of treated and untreated stages IIIa, IIIb, and IV RLF*

	Untreated		*Treated*	*Total*
	Stage III−	*Stage III+*	*Stage III+*	
Satisfactory	11	0	1	12
Myopia unilateral	1	1	1	3
Myopia bilateral	3	1	4	8
Socially blind	0	1	1	2
Totally blind	1	1	1	3
Dead	2	3	1	6
Total	18	7	9	34

Table 5 *Grades of cicatricial RLF found in the eyes of 33 babies who reached stage III RLF or more. Five of these babies subsequently died*

Grade of RLF	*0*	*1*	*2*	*3*	*4*	*5*	*6*
Treated	–	2	8	3	2	2	1
Untreated	4	5	9	2	2	–	–
Unselected	10	4	6	2	–	–	4
Total	14	11	23	7	4	2	5

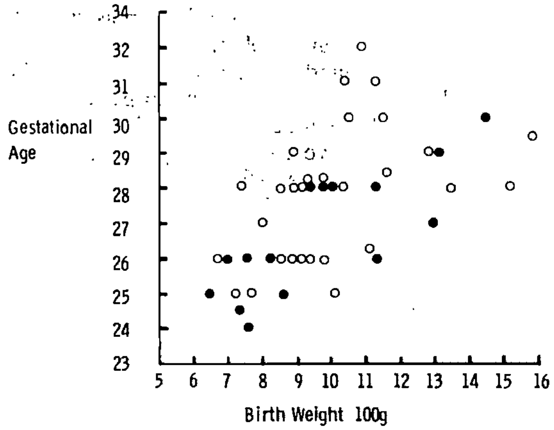

Fig. 1 *Gestational age and birth weight of 45 babies who reached stage III RLF. Those who eventually became blind or highly myopic are shown ●.*

are shown in Fig. 1. The fifteen who now have poor vision are separately marked, and it can be seen that 13 of them had a gestational age of less than 28 weeks, and most weighed less than 1000 g at birth. There was no particular tendency for small-for-dates babies to be more affected than others.

Discussion

The value of treatment in the acute stage of RLF is still not established because of the natural tendency for many cases to undergo resolution without a great deal of scarring, and it is not possible to determine in the early stages which ones will resolve and which will progress. Early reports on treatment were encouraging,[1–4] but later ones have expressed doubt on its efficacy.[5 6] The interpretation of many of the reports is difficult because of the lack of comparable classification schemes, and the established classification of Reese *et al.*[10] does not correspond to the changes seen with the binocular indirect ophthalmoscope. Kingham[11] introduced a practical scheme based on indirect ophthalmoloscopy findings, and this has been modified[9] to accord more with our own observations. Kingham[11] and Bensira *et al.*[7] have used the term acute RLF as synonymous with developing RLF. However, in some of my cases the developing processes were quite slow to evolve, so I have not used this term. Basically Kingham's[11] and Keith's[9] classification agree in that stages (grades) 1–11 developing RLF tend to resolve completely, while stage III is often followed by permanent damage, and stage IV and V are always followed by severe retinal damage. However, we have found that stage III needs to be subdivided into stage III, IIIa, and IIIb, depending on the extent of the circumferential shelf, the degree of vascular engorgement, and the amount of neovascularisation (Table 1). Out of 16 surviving stage III cases 11 have good vision, while only one case which reached stage IIIa or more is thought to have good vision (Table 4).

Treatment of the vasoformative ridge with cryothermy causes a rapid shrinkage of the shelf, with resolution of the proliferative changes in most cases, but significant scarring and retinal drag still occurred. However, it is not possible to say whether the regression would have been so marked without the cryothermy. On one case in stage IV no observable effect was obtained with the cryothermy. The cryothermy in one case that came to post-mortem had produced a satisfactory adhesion between retina and choroid. Laser and light coagulation have not been used in this series, as cryothermy seemed preferable, because of the hazy media and peripheral situation of the lesions. Kingham[5] reviewed the results of treating 12 infants with cryothermy; he concluded that it was probably deleterious or unnecessary and was apparently beneficial only in one case. Ben Sira[7] reported on the good results of treatment, but in his cases the treatment was applied early, mainly in stage II or early stage III, so most of these would be expected to have undergone spontaneous resolution. He treated one eye initially and then treated the following eye if the condition continued to progress. In many of the cases the follow-up was short (20 weeks), and we have found in many of our cases that initially the results were good, but later high myopia developed. Further problems in deciding when to treat are highlighted by 2 babies who did not follow the usual course, as the shelf was only slightly elevated above the level of the retina, with very little general vascular engorgement, but the peripheral changes went on to severe fibrosis and total retinal detachment in one child, while in another it resulted in grade II scarring.

The first 23 cases of stage III RLF (plus 2 cases seen in the cicatricial stage only) were derived from the screening of 358 babies weighing less than 1500 g, giving a prevalence of 7·0%. The overall risk of blindness was small, as this was found in only 3 babies (0·8%). Among the 358 babies seen 86 weighed less than 1000 g; 12 of these reached stage III RLF, one (1·2%) became blind, and 5 (6%) highly myopic.

The danger of visual impairment in surviving premature babies is not very high, but it increases with increased prematurity (Fig. 1) and is quite significant if stage III developing RLF is reached, as out of 28 survivors 5 (18%) were blind. It would seem that, while RLF is no longer a very common cause of blindness within the community, it is still a personal tragedy for the affected child and his parents.

I am indebted to Mrs S. Smith for clinical assistance and Ms Gayle Moore for secretarial help.

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British Journal of Ophthalmology, 1982, **66**, 450–454

Solitary extramedullary plasmacytoma of the palpebral conjunctiva

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SUMMARY A 63-year-old man had a solitary extramedullary plasmacytoma of the conjunctiva for several years with no history of ocular inflammation or systemic abnormalities. Immunoperoxidase staining was consistent with a neoplastic lesion. This is the only well documented such case in the recent literature to the best of our knowledge. This rare condition is contrasted with reactive plasma cell granuloma, a benign inflammatory condition, which comprises most of the cases previously reported as plasmacytomas. Since extraskeletal plasmacytomas may be the first manifestation of multiple myeloma, these patients deserve appropriate diagnostic evaluation and close follow-up.

Plasma cell tumours of the conjunctiva are uncommon. When first described in the early twentieth century they were referred to as plasmacytomas or plasmomas.[1–8] By today's criteria, however, most of these tumours would not be considered true plasmacytomas (rare neoplastic growths consisting of plasma cells) but benign reactive plasma cell granulomas secondary to inflammation.[9 10] True plasmacytomas are rare; they occur most frequently in the upper respiratory tract.[11] An extramedullary plasmacytoma can occur as an isolated lesion or as a manifestation of systemic multiple myeloma. To the best of our knowledge this is the only well documented case of solitary extramedullary plasmacytoma of the conjunctiva in the recent literature.

Case report

A 63-year-old man was first seen by us in September 1978. He had had adult-onset diabetes mellitus for 16 years and was referred by the medical clinic for an ocular examination. He mentioned that he had had a painless 'growth' on his right lower lid for several years and that it had increased only slightly in size. He had also noted decreasing visual acuity in the right eye for a few years. There was no complaint of ocular pain, tenderness, or discharge and no history of ocular inflammation or trauma.

On ophthalmological examination his visual acuity was 6/60 (20/200) in the right eye and 6/24 (20/80) in the left. The middle of the right lower lid was notably swollen. When the lid was everted, a discrete reddish-tan mass measuring 16 mm in largest diameter and 8 mm in height was noted on the palpebral conjunctiva. It was firm, not tender, and adherent to lid tissue along the full length of its base (Fig. 1).

Neither eye showed a papillary or follicular conjunctival reaction. The right upper lid and both left lids appeared normal. There was no bulbar conjunctival injection or discharge, corneal staining, or anterior segment inflammation in either eye. Rubeosis was present in the left eye. Intraocular pressure was 12 mmHg in both eyes. Ophthalmoscopic examination disclosed disc neovascularisation, haemorrhages, and exudates in the posterior pole of both eyes.

After the nature and implications of the patient's problems were explained to him we advised excision of the tumour in the right eye and panretinal photocoagulation for the proliferative retinopathy in both eyes. However, the patient refused any treatment. Then on 16 May 1980 he had a sudden loss of vision in the left eye to 6/75 (20/300). Gonioscopic examination disclosed that rubeosis in the left eye had become more marked and neovascularisation of the angle at the 9-o'clock position was present in both eyes. A vitreous haemorrhage obscured the view of the fundus

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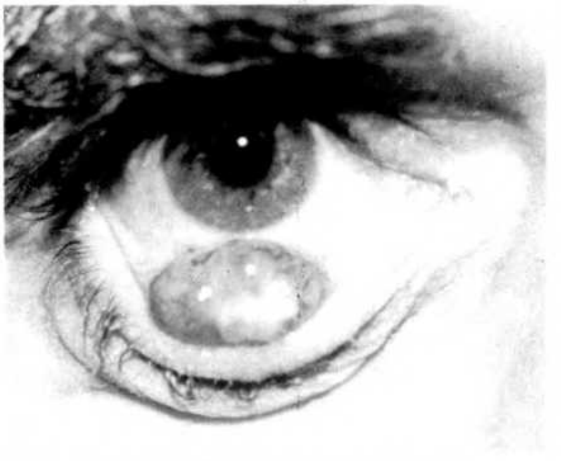

Fig. 1 *Discrete tumour with mottled discoloration involving the palpebral conjunctiva of the right lower lid.*

in the left eye. The lid tumour appeared unchanged, with no evidence of growth. Because of his failing vision the patient then agreed to enter hospital for ophthalmic treatment.

General physical findings included small ulcers over the pretibial areas bilaterally, absent peripheral pulses, grade 2/6 systolic ejection murmur, and peripheral and ulnar neuropathy. There was no lymphadenopathy. Laboratory tests gave moderately raised fasting blood glucose levels which ranged from 140 to 170 mg/100 ml (7·8–9·4 mmol/l). The remainder of his laboratory values were normal; these included white blood cell count of 8×10^9/l with a normal differential count, a haemoglobin of 14·2 g/dl, haematocrit of 40·0%, normal electrolytes, prothrombin time, partial thromboplastin time, chemistry profile, blood urea nitrogen, creatine, and urine analysis. Total protein measured 7·3 g/100 ml (73 g/l) with an albumin of 4·3 g/100 ml (43 g/l). Chest roentgenograms revealed diffuse interstitial markings consistent with early congestive heart failure, which on follow-up roentgenograms had resolved. Electrocardiogram showed normal sinus rhythm and a left bundle branch block.

On 22 May 1980 the patient underwent an excisional biopsy of the lesion of the right lower lid. The most likely diagnosis at this time was a granulomatous nodule, such as a reaction to a foreign body. A scleral graft was placed at the base of the wound. Because of persistent corneal staining the graft was later removed and a conjunctival flap was advanced over the base of the wound.

The tumour was a well circumscribed, oval, pale tan, fleshy mass measuring 15×16×8 mm. Histologically it consisted of sheets of relatively mature plasma cells with characteristic eccentric nuclei and abundant cytoplasm often containing a paranuclear clear space (Golgi space) (Fig. 2). No other cells, such as lymphocytes, histiocytes, or any other type, were present. A Wright-stained touch imprint accentuated the spokewheel configuration of the nuclear chromatin (Fig. 2). Congo red stain for amyloid was negative. Immunoperoxidase staining showed that the plasma cells within the tumour contained cytoplasmic IgM and IgG and lambda light chain only. Electron microscopic examination further confirmed the plasmacytic nature of the neoplastic cells, whose cytoplasm con-

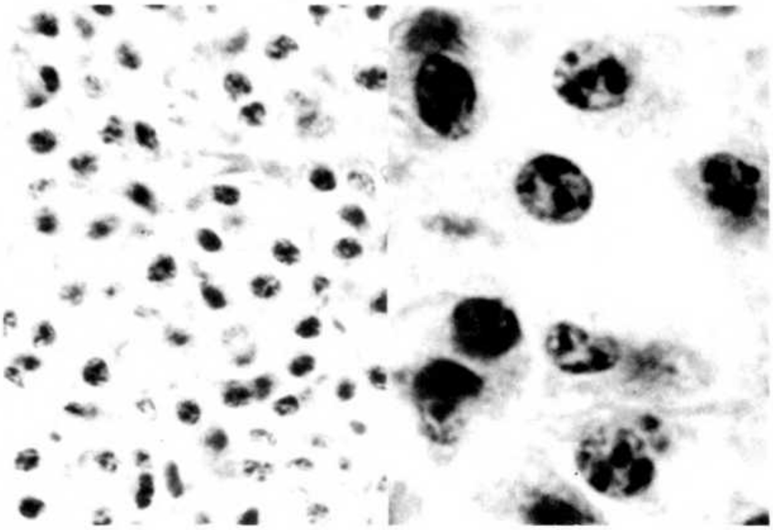

Fig. 2 Left: *Plasmacytoma tissue section showing uniform pattern of plasma cells with characteristic eccentric nuclei. (Haematoxylin and eosin, ×475).* Right: *Touch imprint accentuating spokewheel configuration of nuclear chromatin. (Wright stain, ×1333).*

tained many parallel strands of rough endoplasmic reticulum (Fig. 3).

A systemic examination showed no evidence of multiple myeloma. Bone marrow biopsy revealed normocellular bone marrow with no evidence of plasmacytosis. Serum protein electrophoresis was within normal limits, as were the immunoglobin measurements: IgG 1060 mg/100 ml (10·6 g/l) (normal, 700–1500 (7–15 g/l)), IgA 348 mg/100 ml (3·5 g/l) (normal, 55–350 (0·5–3·5 g/l)), IgM 257 mg/100 ml (2·6 g/l) (normal, 50–265 (0·5–2·7 g/l)). Urine was negative for Bence Jones protein. A bone scan revealed a lesion in the vertex of the skull with more diffuse uptake in the right frontal area. This was consistent with trauma to that area which the patient had sustained several years earlier. Skull roentgenograms, long bone survey, and thoracic and lumbar spine roentgenograms showed no evidence of a lytic lesion. The palpebral conjunctival lesion was therefore classified as an isolated extramedullary plasmacytoma.

During the hospital course the right lower lid healed without complications. The vitreous haemorrhage in the left eye cleared partially and visual acuity improved to 6/15 (20/50). In March 1981 the patient had a sudden loss of vision in the left eye to hand movements. Examination revealed in the left eye a rhegmatogenous retinal detachment with traction; it was repaired by closed vitrectomy and scleral buckling. He is also being followed up in the haematology clinic for evaluation of potential systemic disorders related to the plasmacytoma. In March 1981 his haemoglobin, haematocrit, and serum proteins were within normal limits.

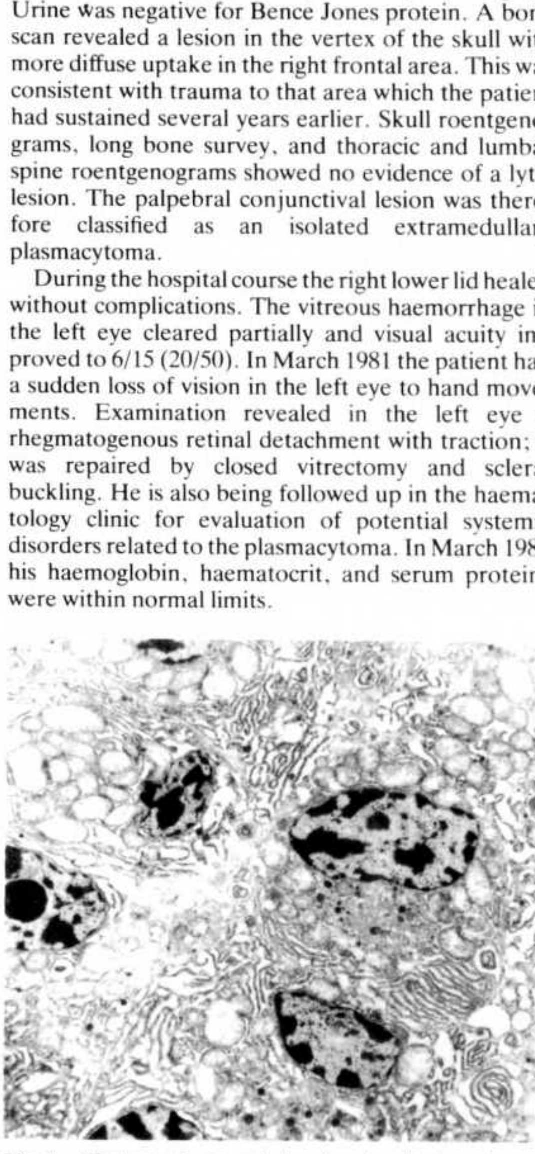

Fig. 3 *Electron micrograph showing abundant rough endoplasmic reticulum of neoplastic plasma cells. (×2800).*

Discussion

Classification of plasma cell disorders is complex. Azar[9] has proposed that plasma cell neoplasms be divided into the following categories: multiple plasma cell myeloma, disseminated nonosteolytic myelomatosis, solitary myeloma, plasma cell leukaemia, lymphoplasmacytic lymphomas, malignant lymphomas with M components, and extraskeletal plasmacytoma. These should be differentiated from benign conditions such as reactive plasmacytoses and plasma cell granulomas. Benign monoclonal and polyclonal gammopathies without evidence of systemic disease can also be included.[12] It is important to distinguish among these categories, as the causes, prognoses, and treatments differ. Particularly when confronted with a plasma cell tumour of the conjunctiva a distinction among 3 entities should be made: (1) manifestation of systemic multiple myeloma, (2) solitary extramedullary (or extraskeletal) plasmacytoma, and (3) plasma cell granuloma.

Multiple myeloma is a systemic disease associated with plasma cell infiltration of bone marrow and usually osteolytic lesions as well as the presence of a monoclonal immunoglobin in serum and/or urine. These patients commonly have anaemia and bone pain, and there may be associated extraskeletal spread of myeloma.

Solitary extramedullary plasmacytomas arise without evidence of solitary myeloma of bone or multiple myeloma. The bone marrow, urine, serum electrophoresis, and haemoglobin are normal at diagnosis of the localised tumour. Abnormal findings with spread of tumour to soft tissue or bone may develop later, at which point the tumour is no longer an independent solitary lesion.[9 13–15] Histologically the tumour consists of sheets of mature plasma cells which may invade surrounding tissue.

A reactive plasma cell granuloma, a benign lesion, is not associated with concurrent or subsequent systemic findings (serum protein abnormalities or bone changes). It is induced by an inciting foreign antigen having produced previous inflammation and is adequately treated by excision. Histologically it is composed not only of mature plasma cells but also of histiocytes, lymphocytes, eosinophils, fibroblasts, and capillary endothelial hyperplasia. The term 'granuloma' has also been used for reactive lesions even in the absence of histiocytes.

Plasma cell tumours of the conjunctiva were reported occasionally in the early twentieth century as 'plasmomas' or 'plasmacytomas.' These cases, however, were documented with inadequate clinical and laboratory evaluations. Most authors believed chronic inflammation to be the cause.[1–8] In fact most cases occurred in patients with trachoma, and all occurred in endemic trachoma regions. In 1915 Verhoeff and Derby reviewed the literature on plasmacytoma and concluded that 'the evidence at hand points to an inflammatory origin for this condition. The clinical fact that it has occurred frequently in conjunctiva showing evidence of existing or previous trachoma points in this direction.'[7] Most later reports of conjunctival 'plasmacytomas' also suggest inflammation as the cause.[16–19] Most of these lesions would be classified today as plasma cell granulomas. For this reason Dolin and Dewar did not include cases involving the conjunctiva in their review of extramedullary plasmacytomas.[20]

One well documented case involving the conjunctiva resembles a true plasma cell neoplasm that occurred with an orbital mass as a terminal event in a patient with known multiple myeloma.[21] Jampol and associates described a lymphoplasmacytic tumour of the conjunctiva associated with systemic lymphoma and a monoclonal IgA gammopathy.[22] Plasma cell infiltration appearing as diffuse thickening of the conjunctiva or conjunctivitis rather than a discrete mass has also been noted.[23,24] In one of these cases a mixed cellular infiltrate was associated with cytoplasmic crystals consisting of IgG.[23] The other case, according to the authors,[24] probably represented a reactive chronic inflammatory response rather than neoplasia.

In contrast the patient described here had a fairly well circumscribed mass with no history of ocular inflammation or medical illness. Histopathological examination revealed a lesion consisting of only sheets of mature plasma cells without a mixed cellular population and no fibrovascular proliferation. The finding of only lambda light chain on immunoperoxidase staining supported the diagnosis of neoplasia. The presence of more than one heavy chain, as in our case, has been reported in rare cases of myeloma.[25] Clinical, haematological, biochemical, and radiological investigations ruled out systemic disease. This lesion therefore meets the diagnostic criteria for a true solitary extramedullary plasmacytoma of the conjunctiva. Long-term stability of both symptoms and myeloma protein production may occur in patients with indolent myeloma and in those with localised plasmacytoma.[26] The long history of the lid lesion which remained localised in our case is therefore not inconsistent with the diagnosis of plasmacytoma.

Solitary extramedullary plasmacytoma of the orbit, as of the conjunctiva, occurs rarely.[27] Somewhat more common are plasma cell pseudotumours[28] and orbital plasma cell tumours which represent an extraskeletal manifestation of multiple myeloma.[28–30] In the latter category in 23 of the 30 patients studied by Rodman and Font proptosis was the initial manifestation of the disease.[28]

The diagnosis of plasmacytoma rather than plasma cell granuloma is liberally applied to a number of plasmacytic growths at other sites. 80% of the reported 'extramedullary plasmacytomas' develop in the oral cavity or respiratory tract.[31] Some of these, however, may be benign inflammatory processes even though they appear as a discrete mass.[9] Following in frequency are plasmacytomas involving the gastrointestinal tract and lymph nodes.[15,32] Skin and soft tissue are more rarely involved.[33]

Not only do the causes differ but prognosis and treatment of plasma cell disorders also vary. Unlike reactive plasma cell granuloma, extramedullary plasmacytoma is considered to be of low-grade malignancy, and the clinical course after excision is not entirely benign. Studies of nonocular cases have shown that multiple myeloma may develop after several months or even years in up to 30% of cases.[34,35] Involvement of lymph nodes and development of new foci of tumour cells in soft tissue and bone can occur.[13,34] Treatment for both plasmacytoma and plasma cell granuloma consists of excision, but radiotherapy is recommended in addition for the neoplastic growth.[36] Although no such cases have been reported, it is conceivable that patients with extraskeletal plasmacytoma of the conjunctiva may also subsequently develop systemic manifestations of multiple myeloma. Therefore periodic systemic evaluation is warranted. We decided to follow up our patient closely after complete excision of the tumour rather than to treat him with radiotherapy.

We thank Ingrid von Saltza for help with translations.

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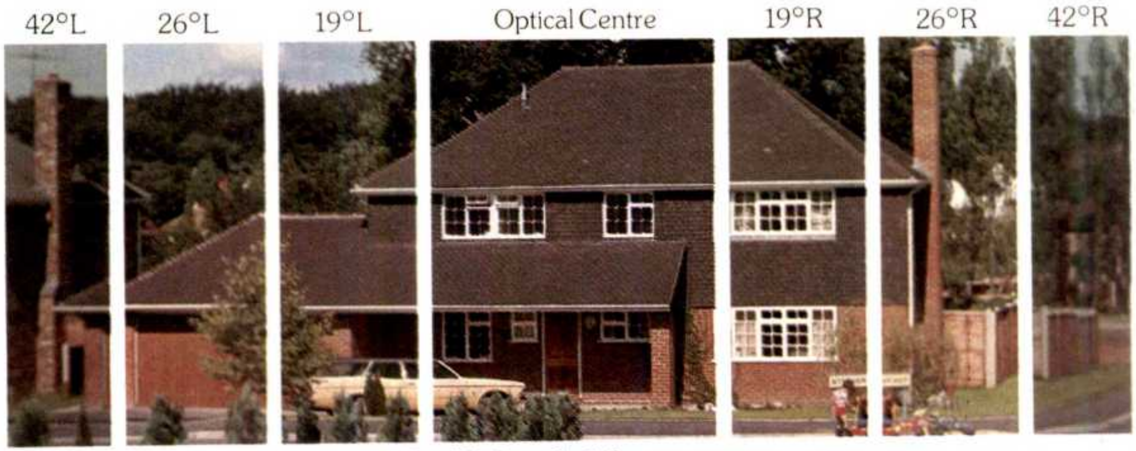

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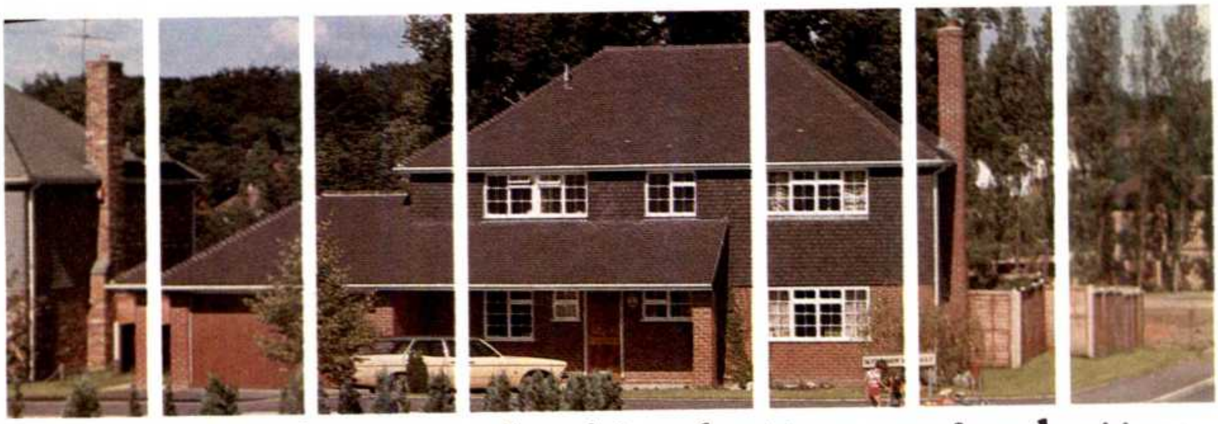

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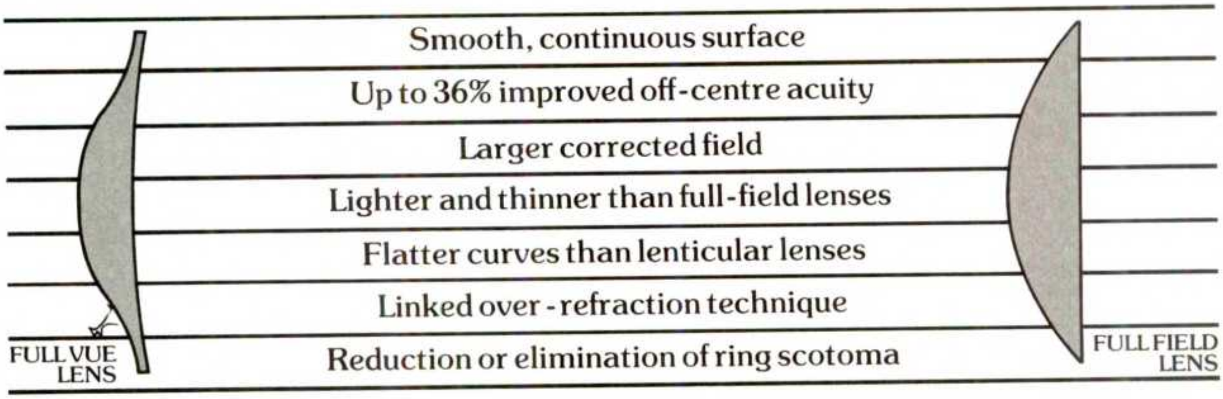

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British Journal of Ophthalmology, 1982, **66**, 455–463

Congenital tumours of the anterior visual system with dysplasia of the optic discs

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SUMMARY The occurrence of dysplastic optic discs in young patients with tumours involving the anterior visual pathway not only may provide a valuable diagnostic sign but also bears witness to the early prenatal origin of these tumours.

An optic disc may be considered to be dysplastic when it is congenitally abnormal owing to a developmental abnormality. Gross anomalies include colobomata and pits, and the optic disc may be of abnormal size, an unusual shape, or have an abnormal vascular arrangement. Minor developmental anomalies include unusual pigmentation or abnormalities of the peripapillary retina. Small dysplastic or hypoplastic discs may be difficult to diagnose, since there are no absolute criteria and no readily available techniques for measurement. Clinical judgment can be enhanced by evaluation of the ratio between the apparent size of the disc and the retinal arterioles or the size of a disc relative to the size of the fundus in a standard fundus photograph, but even with these techniques the vagaries of observation leave the diagnosis to the clinician alone. Anomalies of the outline and vasculature have to be obvious to be considered abnormal, but there are no definitive criteria. The incidence of congenital optic disc anomalies in the population is impossible to assess, but Duke-Elder[1] considered them to be rare in their gross forms, and Riise[2] estimated that a common type of optic disc anomaly, the inferonasal conus, occurs in 1% of the population.

Congenitally abnormal optic discs have been reported with bitemporal visual field defects, unassociated with disease of the nervous system,[2–5] suggesting a concomitant chiasmal anomaly. Anomalous optic discs in patients with suprasellar tumours have been considered[2 4 6 7] to be an incidental association. These authors reported 6 cases, and of the 2 patients in whom the pathology was recorded one had a dysgerminoma and clearly congenitally abnormal discs, and the other had a pituitary adenoma and an abnormal optic disc on one side. The latter patient was aged 19, and it is interesting that only 2·4% of 1000 chromophobe adenomas in the Mayo Clinic series[8] were below 20 years old. Keane[6] also pointed out that this patient had a monocular hemianopic scotoma, found only in 2% of the Mayo Clinic series. The monocular hemianopic scotoma was in the eye with the abnormal optic disc—clearly an unusual case. Keane[6] points out that the relationship of the visual field defect to the midline and a careful fundus examination will distinguish clinically between the cases with chiasmal compression and those with an isolated dysplastic optic disc.

This paper describes 7 children with dysplastic optic discs associated with a suprasellar tumour of presumed prenatal origin, and suggests a causal relationship. These cases form part of a series of 23 patients presented previously.[9] Most of the patients had complicated histories, so that details relating to the visual system and the diagnosis only will be included.

Case histories

CASE 1

A girl born in April 1966 was well until December 1973, when her parents noticed bulging of her left eye. In January 1974 she had an acuity of 6/6 right eye and 6/12 left eye (plano right eye −0·75 cyl 170° left eye). By June 1974 the acuity of the left eye had deteriorated to 6/24, and a mildly swollen left optic disc was noted. She had an enlarged optic canal on the left. Cosmetic left medial rectus surgery and an optic nerve biopsy were performed at another hospital. The histological examination showed a low-grade

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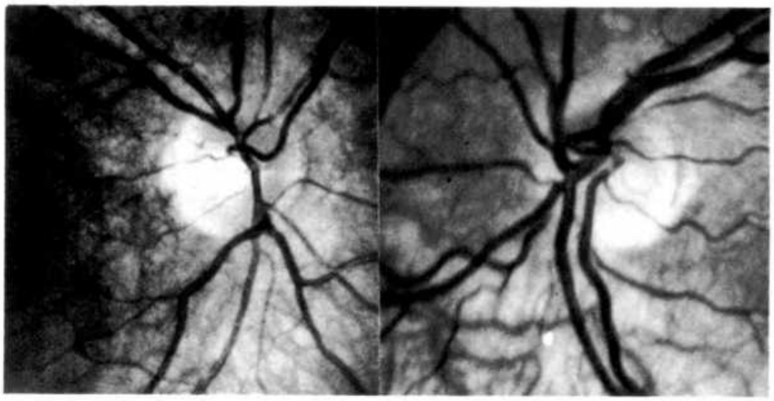


Fig. 1 *Case 1. The fundi in October 1977. The right optic disc is normal but the left is segmentally hypoplastic or tilted. There was a glioma of the left optic nerve.*

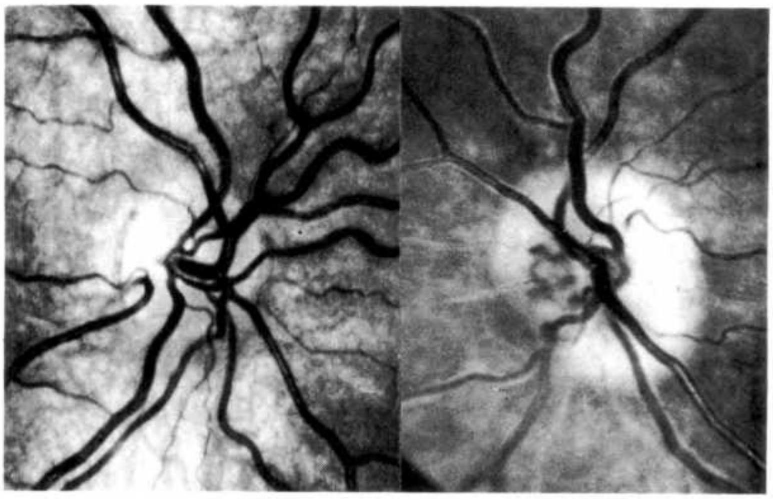


Fig. 2a *Case 2. The fundi in May 1976. There was a glioma of the chiasm and left optic nerve. The left disc was small and tilted, with shunt vessels. The right disc was substantially normal, but the presence of a temporal hemianopia is suggested by the presence of a horizontal band of relative optic atrophy.*

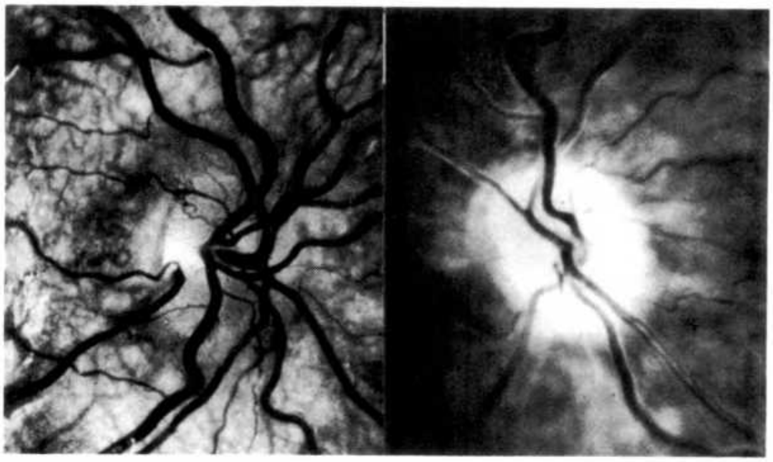
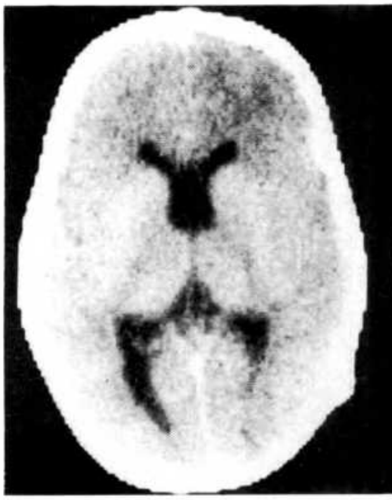


Fig. 2b *Case 2. The fundi in January 1978. The left disc is now totally atrophic but still tilted, while the right shows a bilobulated papilloedema that corresponds to the intact nerve fibres subserving the nasal visual field.*



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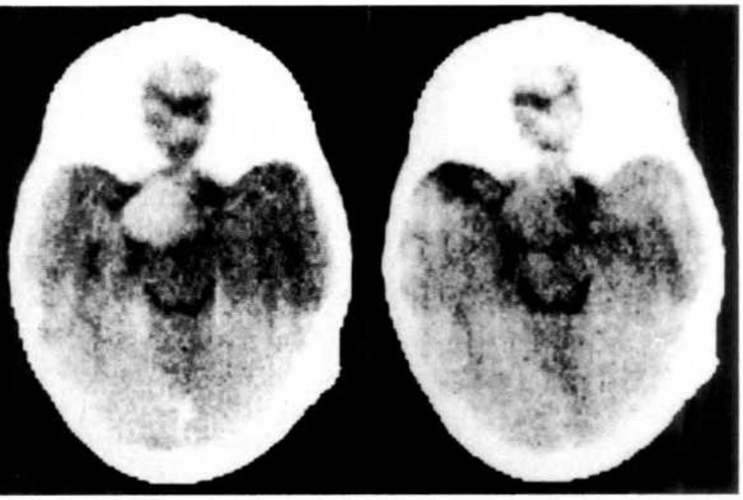


3b

Fig. 3a *Case 3. CT scan through the ventricles showing absence of the septum pellucidum.*

Fig. 3b *Case 3. CT scan through the suprasellar cistern shows a small mass towards the left hand side. On the left is the scan after enhancement, demonstrating its vascularity. A biopsy was not carried out owing to the child's stable condition since infancy.*

glioma. In April 1975 the left acuity was 4/60, improving to 6/60 with correction (+7·50 cyl 90°). She had gross proptosis and the left optic disc was seen to be pale and tilted (Fig. 1). The optic nerve was subsequently removed by a combined orbital and subfrontal approach.

CASE 2

A girl born in April 1968 had developed a squint by 1973, which ultimately led to the diagnosis of a suprasellar and left optic nerve tumour, proved on biopsy to be pilocytic astrocytoma.

The left eye had had very poor vision since she was first seen and in 1976. The acuity was 4/60 unaided, and shunt vessels were noted on the small, tilted disc (Fig. 2a). There was no refractive error. From 1974 she had a gradually increasing temporal visual field defect in the right eye, and by 1977 this was absolute. In 1978 she had an episode of raised intracranial pressure which gave the appearance of twin peaks of papilloedema in the right eye, while the left optic nerve showed 'total' atrophy and loss of nerve fibres (Fig. 2b). She became blind at that time but regained some vision after a shunt operation.

CASE 3

In 1979 this 6-year-old girl of Portugese extraction was seen by Mr M. D. Sanders, of the National Hospital, Queen Square.

The limited history available was that her parents noticed her vision was reduced when she was 2 months old, but she seemed to see enough to follow objects. When she was 5 months old she had 2 ventricular shunts for hydrocephalus. At 5 years old she was noted to have very poor vision in the right eye and limited vision in the left eye. She had no other symptoms. On examination she was just able to identify objects with the right eye but had 6/60 acuity in the left; the visual fields were grossly constricted. Both optic discs were obviously hypoplastic, the right one having a figure of 8 outline (Fig. 3c). A CT brain scan showed absence of the septum pellucidum (Fig. 3a) and a suprasellar mass (Fig. 3b). No further treatment or biopsy was performed.

CASE 4

This boy was born in 1958 and his early life was uneventful.

In 1975 he was investigated for short stature and delayed puberty and suprasellar calcification was shown. In 1977 his vision deteriorated and he had headaches. His corrected acuity was 6/5 right eye (−4·0 sphere) and 6/4 left eye (−4·50 sphere). He had a bitemporal hemianopia. Bilaterally hypoplastic and tilted discs were noted (Fig. 4). A clinical diagnosis of craniopharyngioma was made, and this was subsequently confirmed by histopathology when subtotal excision was performed, followed by radiotherapy.

CASE 5

This girl was born in March 1970 and was noted at

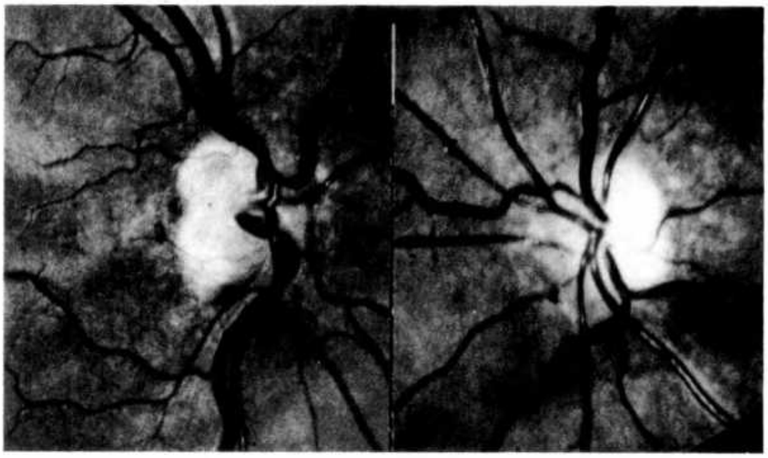


Fig. 3c *Case 3. Both optic discs are hypoplastic, and that on the right has a figure of 8 outline, suggesting that there may have been a congenital temporal hemianopia.*

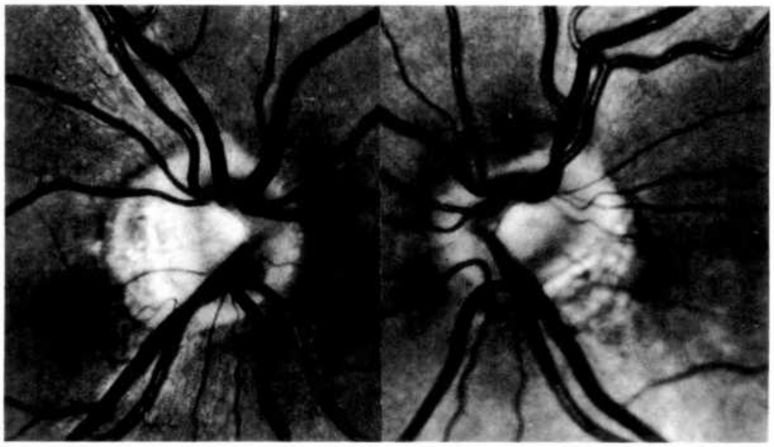


Fig. 4 *Case 4. The fundi in April 1977 now had bilaterally tilted optic discs, especially on the left side, which was significantly hypoplastic. The patient had a craniopharyngioma.*

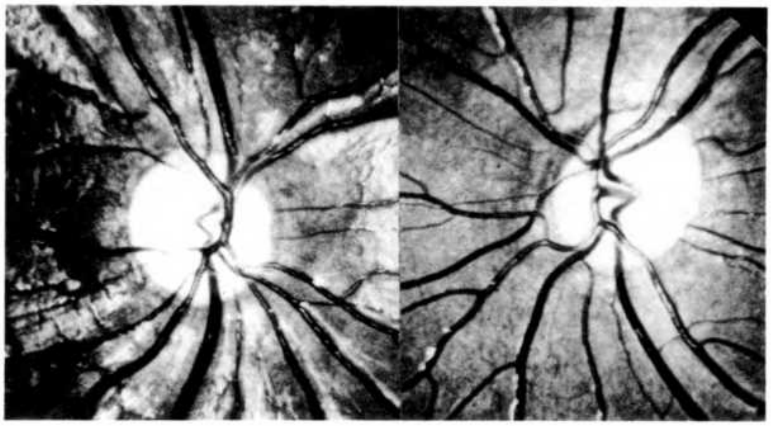


Fig. 5 *Case 5. The fundi in December 1977 showed gross optic atrophy and thinning of the retinal nerve fibre layer. The left optic disc was oval and somewhat irregular in outline. The patient had a chiasmal glioma.*

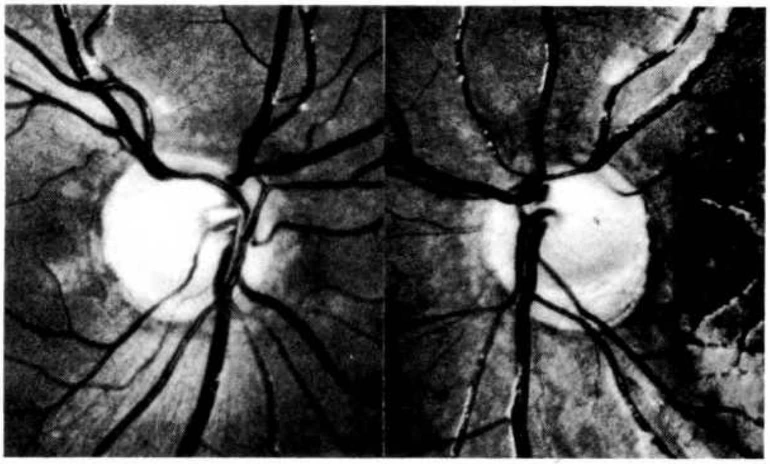


Fig. 6a *Case 6. The fundi in March 1975 show that both discs are pale and both abnormal in outline, the left being definitely segmentally hypoplastic or tilted. In the right eye it is possible to see clearly the presence of some nerve fibres above and below the optic disc. She had a bitemporal hemianopia.*

birth to have dermatological signs of von Recklinghausen's disease. In 1977 her vision was found to be defective at school, and in December 1977 at the Hospital for Sick Children, Great Ormond Street, she had an acuity of 3/36 in the right eye and 3/60 in the left. There was no refractive error. A bitemporal hemianopia was noted. A CT brain scan showed a suprasellar mass, and both her discs were atrophic, with the left disc having an oval, irregular outline (Fig. 5). She was ultimately transferred to another hospital and had a biopsy, which showed a fibrillary astrocytoma.

CASE 6

This girl was born in October 1964 and suffered no symptoms until she was 10 years old, when she suddenly lost vision. The cause of this was found to be a craniopharyngioma, which was histologically confirmed on several occasions. She had several operations and a course of radio-therapy. In 1975 she had a bitemporal hemianopia and acuities of 6/36 right eye and 6/8 left eye with no refractive error. Bilateral tilted discs were noted (Fig. 6a). In July 1978 she became drowsy and was found to have papilloedema (Fig. 6b), which on fluorescein angiography of the right eye was seen to be of bilobular appearance (Fig. 6c); both optic discs were atrophic and tilted. After a shunt operation her symptoms improved, but after further surgery on 21 July 1978 for gross enlargement of a cystic space she became totally blind, with no pupil reaction to light. She remained blind until October 1979, when she stated that she could see better than before; she had had a profound religious experience some months previously. On examination

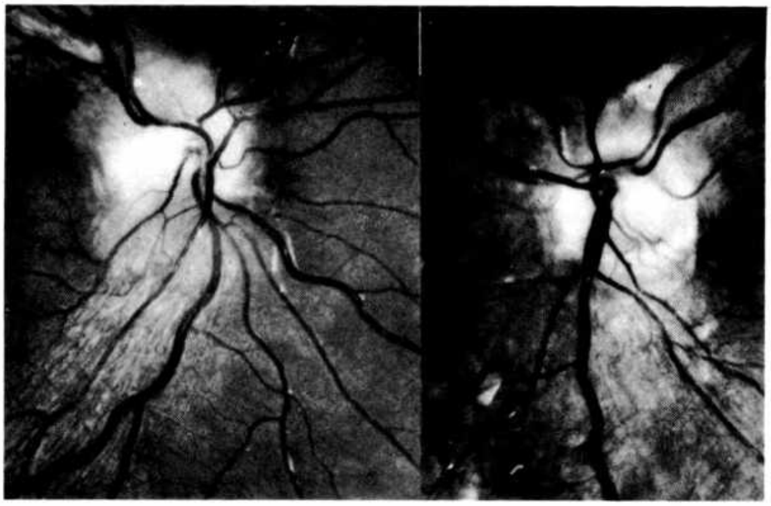
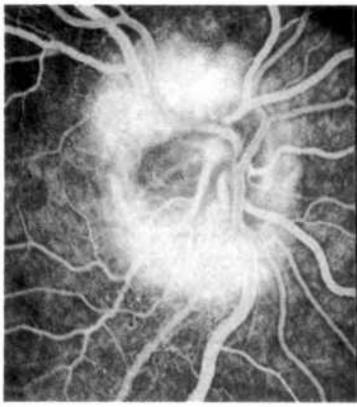


Fig. 6b *Case 6. The fundi in July 1978 show bilateral swelling of the remaining nerve fibres of the upper and lower poles due to raised intracranial pressure.*



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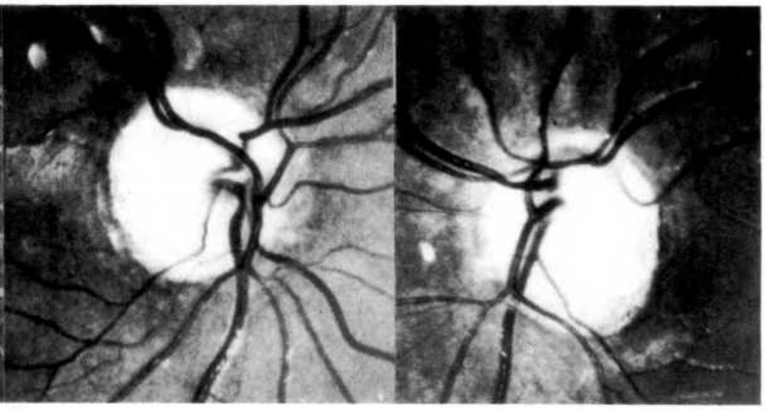

6d

Fig. 6c *Case 6. A fluorescein angiogram of the right optic disc in July 1978 showed dilatation of the peripapillary capillary plexus and leakage of fluorescein of the upper and lower poles, which are the areas corresponding to the insertion of intact retinal nerve fibres from the area subserving the nasal half field.*

Fig. 6d *Case 6. The fundi in October 1979. Although the patient appears to have total optic atrophy and at this time had no perception of light, she later regained 6/12 acuity in the right eye, with an extremely small visual field.*

in July 1981 she was able to see 6/12 with the right eye $\left(\frac{-2{\cdot}0}{-0{\cdot}50\ 180}\right)$ but had no perception of light with the left eye $\left(\frac{-0{\cdot}50}{-}\right.$ retinoscopy$\left.\right)$. She was able to read 6/9 near equivalent. Her remaining visual field was so small as to be of little value to her in moving about. Both discs were grossly atrophic and tilted.

CASE 7

This 32-year-old man of Middle Eastern extraction was seen on one occasion in June 1981. He had von Recklinghausen's disease and a tumour involving the suprasellar cystern and the left optic nerve. The left eye had no perception of light and the right 6/5 corrected acuity (+0·50 cyl 180°). There was no refractive error in the left eye. He had normal colour vision tested with Ishihara plates and normal visual fields in the right eye. Both optic discs had a somewhat irregularly oval outline, and there was an anomalous arteriole in the superonasal quadrant of the atrophic left disc.

Discussion

Of several tumours affecting the anterior visual pathway in childhood gliomas and craniopharyngiomas are the most commonly encountered.[10] Both of these tumours are thought to arise from developmental anomalies dating from embryonic life.

Craniopharyngiomas are benign tumours that arise very early in development from the blind-ended pouch described by Rathke[11] 150 years ago. Rathke's pouch appears on the 21st day of life and becomes a

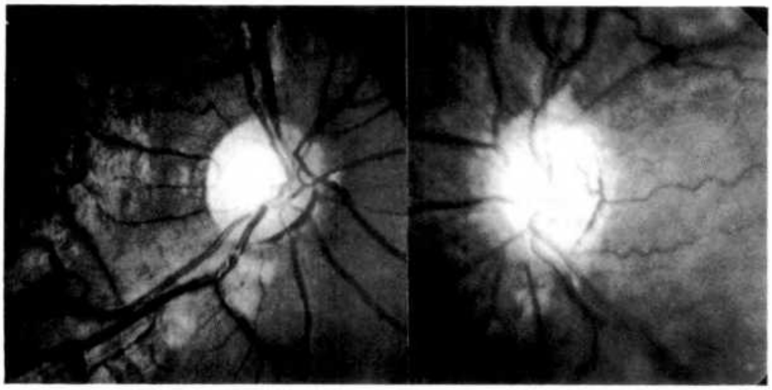

Fig. 7 *Case 7. The fundi in June 1981. Both optic discs are irregularly oval in outline and the left optic disc is slightly smaller than the right. In addition the left optic disc shows an anomalous arteriole. The patient had a presumed optic glioma.*

blind-ended tube with its fundus near the developing diencephalon, chiasm, third ventricle, and neurohypophysis. The infundibulum or stalk becomes closed off by the 47th day; there is evidence of this connection even in adult life in that craniopharyngiomas are found outside the hypophysis. Both the extrahypophyseal location of craniopharyngiomas and their adamantinomatoid structure generally argue in favour of their early embryological origin,[12] a view advanced by Erdheim[13] in 1903.

Hudson[14] originally indicated that optic nerve gliomas were benign, but there has been much discussion recently on the pathology of visual pathway gliomas. However, most authors believe that in childhood they lack malignant features[15] or are a benign type of pilocytic astrocytoma.[16] They generally behave in a benign manner on tissue culture.[17] It has been proposed that they are a form of developmental abnormality or hamartoma.

There have been several recent summaries of the embryology of the eye,[18–22] and its course in the first 2 months was detailed by O'Rahilly,[23] who examined 100 sectioned embryos whose development had been carefully staged.

Although crown-rump length (CRL) and gestational age (GA) are time-honoured and familiar in principle to most ophthalmologists, each of these measurements is subject to its own special imprecision. CRL is influenced greatly by the method of measurement, the extent of flexures, and the amount of shrinkage in preparation, and GA is as imprecise as the vagueness of the time of conception. Staging based on internal and external criteria, particularly in the early stage the number of somites, is frequently used as a more reproducible measurement.[24] Originally known as developmental horizons, stages I-XXIII were described, stage I being the unicellular organism and stage XXIII heralding the end of embryonic development and the beginning of the fetal phase. By stage XXIII the fetus is well developed, with clearly defined organs, and the eyelids are nearly closed. O'Rahilly[25] has been responsible for staging development up to stage IX.

The first clear evidence of a precursor of the human eye is found in the 8 somite stage X embryo (GA approximately 22 days, CRL approximately 2·2 mm). The 2 primordia appear on either side of a notch in the anterior end of the neural tube. These thickenings in the neural tube are joined by a primitive chiasma, the torus opticus. In invertebrates there is evidence that there is cross-over of some fibres at this stage.[26] The primordia became evaginated to form a pair of vesicles which contact the overlying ectoderm by stage XIII (GRL 4·5, GA 26). The retina becomes distinguishable by stage XIV, when there is a clear differentiation between the optic stalk and the cup which ultimately forms the eye; it is notched below (the fetal fissure) for the entry of vessels. The cup closes beginning at stage XVI and is well advanced by stage XVII (CLR 12, GA 40). By stage XIX nerve fibres from the ganglion cells are growing back down the stalk, which is also soon surrounded by a cellular sheath. The optic nerve fibres cross the chiasm and reach the brain by stage XXL, and they become well defined around the area behind the optic disc by stage XXIII, at which time the optic nerve is surrounded by a thick sheath.

Thus by stage XXIII the optic nerve has its full complement of retinal ganglion cell axons, a well defined optic disc with an opening in the sclera that is contiguous with the optic nerve sheath. This is a gestational age of about 50 days and a crown rump length of between 27 and 31 mm. It is uncertain when the scleral opening in the optic canal attains its final form, but Duke-Elder and Cook[27] imply that this has occurred by the fifth month of gestation. Substantial congenital anomalies of the outline of the optic disc will have occurred by that time at the latest.

The patients described in this series all had optic discs that were congenitally abnormal (dysplastic) either in size, outline, vascular arrangement, or a combination of these. The degree of abnormality was greater than the commonly found conus defects, and if a conus was present it was not the only defect in in these cases.

Patients 1, 4, and 6 had small optic discs that were abnormal in a way that has variously been known as a crescent, conus, diversion, or situs inversus; these abnormalities may be grouped and called tilted,[28] but they were also smaller than normal. They should be distinguished from the acquired disc abnormality that is commonly seen in myopia,[29] although not infrequently they are myopic.

Mann[29] pointed out that if one excluded the common (usually acquired) temporal crescent, nearly 70% of crescents occur inferiorly in the disc, and that a further 12% occur inferonasally or inferotemporally. Mann suggested that this predominantly inferior portion of the crescent indicated an origin from an anomaly of closure of the fetal fissure, and she thought that it was due to a germinal failure of the retinal pigment epithelium to reach the site of junction of the optic stalk with the cup. Dorrell[28] pointed out that the retinal opening at the optic nerve head was often circular and the outline of the scleral canal was contracted across one segment, giving rise to a D shape. In many cases the whole disc was D shaped, and in other cases there appeared to be fewer nerve fibres in the retina adjacent to the crescent. These abnormalities are of prenatal origin. Dorrell suggested that many cases of tilted discs represented a form of segmental hypoplasia, and he pointed out the similarity between the double ring sign in optic disc hypoplasia and the appearance of the crescent.

The retina is first supplied by vessels that come through the fetal fissure during stage XIV, and the central artery and vein are clearly apparent by the third month of gestation. By the seventh to eighth month the hyaloid system has degenerated, leaving the barest remnants, and it seems likely that the pattern of the central retinal artery, vein, and their branches take their life-long pattern at this stage. Venous shunt vessels as seen in patient 2 are almost certainly acquired in postnatal life, whereas the arterial abnormalities in patient 7 are more likely to be abnormal at birth, and probably several months before that.

The optic discs of patients 3 and possibly 4 were frankly hypoplastic. The diagnosis of hypoplastic optic discs is very subjective, because there is no ready way of measuring the optic disc clinically or of estimating the number of optic nerve fibres entering the optic disc. If one accepts these limitations, careful observation of the optic disc and the retinal nerve fibre layer can allow a reasoned diagnosis of minimal optic disc hypoplasia to be made.[30] Frisen and Holmegaard[30] pointed out that symmetrical involvement makes diagnosis difficult, and they drew attention to other pitfalls in diagnosis such as the unreliability of the double ring sign. Although at the Hospital for Sick Children we have seen several other patients with optic gliomas or craniopharyngiomas who have lesser degrees of hypoplasia, they have not all been included in this series, though an example of a minimal abnormality is seen in case 5.

Not only were the optic discs in case 3 small but one also had a figure of 8 outline. Although it was impossible to carry out a visual field examination in this child, it is likely that she had a bitemporal hemianopia and at the very least a suprasellar tumour. Both of this child's optic discs may be analogous to the optic disc with the temporal field defect in congenital homonymous hemianopia.[31] The fibres destined to cross in the chiasm either failed to do so or crossed and then died back in prenatal life, leaving the intact fibres from the temporal retina to insert themselves into the upper and lower parts of the disc, the nasal and temporal parts of the disc failing to develop.

These findings should suggest to the clinician that, when he finds a visual defect in patients with dysplastic optic discs, he should pay careful attention to the visual field examination when the patient is old enough to perform it in detail, and that a CT scan may be indicated because the cause may be a congenital but progressive tumour with devastating, but preventable, consequences for the future wellbeing of his patient.

I am grateful to Mr Michael Sanders, FRCS, of the National Hospital. Queen Square, for permission to publish details of case 3, to Mr Rolfe Sennhenn and Mr Martin Johns for their photographic skills and kindness to the patients, and to Anna Taylor, who prepared the drafts and manuscript.

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British Journal of Ophthalmology, 1982, **66,** 464–470

Glaucoma patients not compliant with their drug therapy: clinical and behavioural aspects

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SUMMARY The pattern of drug self-administration among 15 patients not compliant with their pilocarpine therapy was studied with an electronic medication monitor. Recording the date and the hour every time the medication bottle was opened, the monitor gives detailed information on the medication behaviour. The results indicate different types of medication errors: inadequate spacing of doses during the day with long intervals during the night, frequently missed doses at noon, and long interruptions in the medication, sometimes lasting for several days. Improvement in their compliance was seen in patients who were given instruction and taught to relate their medication to specified events in the day.

Noncompliance with prescribed drug regimens has been noted among patients on long-term medication for many chronic diseases, including glaucoma.[1–10] Unfortunately it is often difficult to compare different investigations owing to the lack of uniformity in the definitions of compliance. With 2 or more missed doses a week as a definition of non-compliance Bloch *et al.*[7] found that 11 (28%) out of 40 patients on drug treatment for glaucoma did not comply with the therapy. In a similar study by Vincent[4] 58% of 62 patients did not adhere to their glaucoma therapy, but in that study only one missed dose a month was permitted for a patient to be termed compliant. In a previous study[10] we found that 41% of 82 glaucoma patients on pilocarpine 3 times daily missed 6 or more doses during a 20-day period. An 8-hour dose interval was exceeded at least 20% of the time by 43% of the patients.

In comparison with the extensive work on other aspects of compliance with drug therapy little is known about the pattern of drug self-administration. This may be partly due to the lack of appropriate methods of measurement giving objective and detailed information on the medication behaviour. Yee *et al.*[6] used a medication monitor to study drug self-administration by 2 glaucoma patients on pilocarpine therapy. Both patients on q.i.d. (4 times daily) prescription missed a large number of doses, and one of them never used the drug more than 3 times a day during the 3 weeks studied. Except for the morning dose these patients spaced the times of medication during the day rather erratically, with marked variation of dose intervals. Kass reported similar results in a preliminary study of 38 glaucoma patients.[8] He also found a wide range between patients in their compliance with the regimen and a considerable variation from day to day in some of them.

The effect of strategies to improve compliance has been evaluated in many clinical trials. The results diverge between different strategies and different settings.[11] A striking finding is that increasing the patient's knowledge about his illness and its treatment does not always lead to improved compliance.[12] However, tailoring of doses to 'daily events of a reinforcing nature, may be an important way of helping patients to remember to take their medication.[13]

The purpose of this study was to describe the pattern of drug self-administration by 15 non-compliant patients with open-angle glaucoma (OAG) on pilocarpine therapy and to evaluate the effect of an education and tailoring programme given to 8 of them.

Patients and methods

METHODS

Self-medication with pilocarpine eye drops 3 times a day was studied with an electronic medication monitor previously described.[14] The monitor

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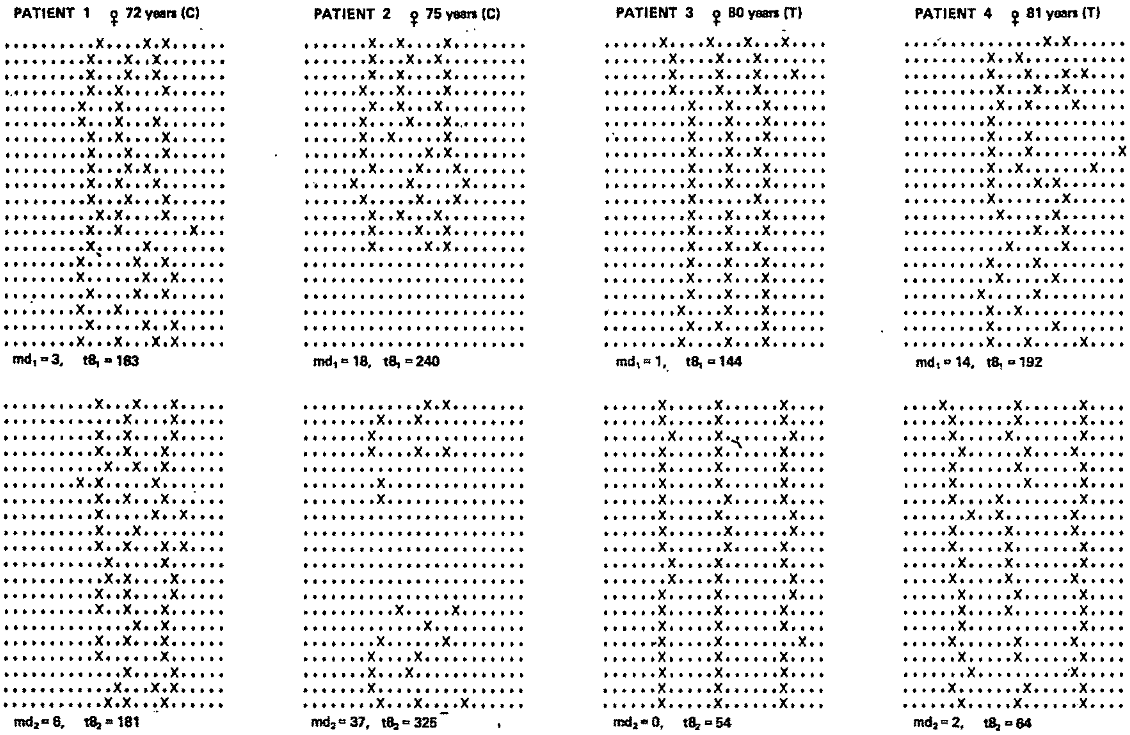

Fig. 1 *For legend see Fig. 2.*

recorded the date and hour every time the medication bottle was opened during 3 weeks between visits to the eye clinic. The monitor data from the days of the clinic visits were excluded, leaving a record of 20 days. At the end of the first monitor period, patients randomly allocated to a trial group took part in an education and tailoring programme with the aim of improving their compliance. This programme is described elsewhere.[15] The rest of the patients acted as controls. The medication behaviour of all patients was recorded during a second 20-day monitor period. The patients were interviewed at the end of this period. The interviews earlier described[16] included the following questions:

(1) How many times a day do you take this drug (pilocarpine)?

(2) How often does it happen that you don't take one of these doses?

(3) How many times did this happen during the past 7 days?

(4) Do you take the eye drops yourself or do you get help from any other person? If Yes to the second part of the question, How often does it occur?

(5) Do you take your eye drops in connection with any special event during the day, the first–second–third time? If Yes, What special event?

We wanted to get information about spontaneous tailoring of doses among patients included in the trial group, before they went through the education and tailoring programme. Therefore the last question was put to these patients at the end of the first monitor period immediately before the presentation of the programme.

Measurements of intraocular pressure (IOP) were included in a routine clinical examination at the end of the first and second monitor periods. The monitor data from the days of clinic visits, although not shown in the monitor records of this paper, were noted for each patient. With the information on the times for clinic visits the number of hours since the last drug administration could be calculated.

MEASURES OF COMPLIANCE

The number of missed doses during the first 20-day monitor period (md_1), was calculated for each patient (that is, the sum of the number of doses less than 3 each day). Dividing this number by 60 (the total number of doses prescribed) gives the proportion of missed doses (pmd_1).

If all the prescribed doses were taken at equal intervals, the interval length would have been 8 hours. For each patient the time exceeding an 8-hour

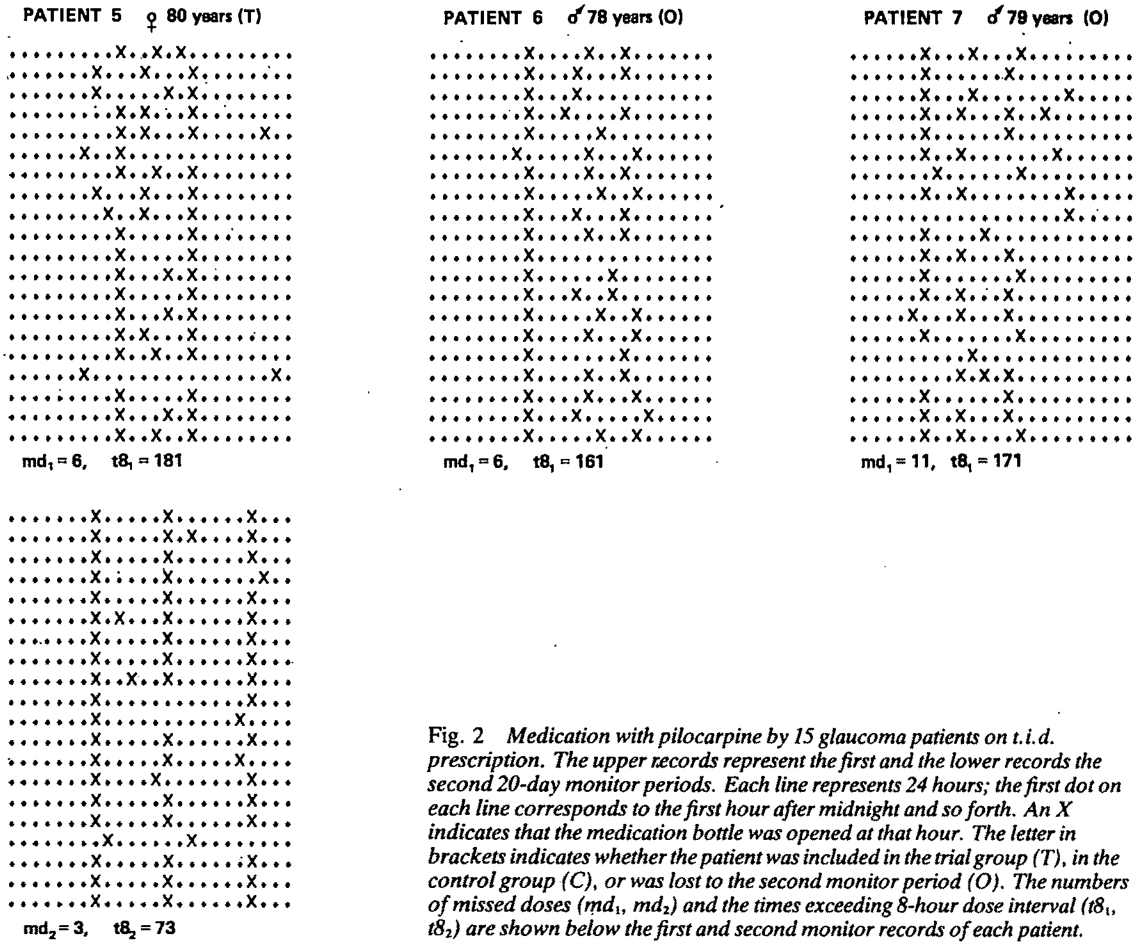

Fig. 2 *Medication with pilocarpine by 15 glaucoma patients on t.i.d. prescription. The upper records represent the first and the lower records the second 20-day monitor periods. Each line represents 24 hours; the first dot on each line corresponds to the first hour after midnight and so forth. An X indicates that the medication bottle was opened at that hour. The letter in brackets indicates whether the patient was included in the trial group (T), in the control group (C), or was lost to the second monitor period (O). The numbers of missed doses (md_1, md_2) and the times exceeding 8-hour dose interval ($t8_1$, $t8_2$) are shown below the first and second monitor records of each patient.*

dose interval was calculated for the first 20-day monitor period ($t8_1$). Dividing this sum by the length of this observation period gives the proportion of time exceeding 8-hour dose interval ($pt8_1$).

PATIENTS

The study sample included all patients from a previously described series of 82 patients with OAG on 4% pilocarpine eye drops 3 times a day (t.i.d.), who fulfilled at least one of the following criteria: (1) a proportion of missed doses during the first monitor period of at least 25% ($pmd_1 \geq 25\%$); (2) a proportion of time exceeding an 8-hour dose interval of at least 30% during the first monitor period ($pt8_1 \geq 30\%$).

One or both of these criteria were fulfilled by 15 patients. Their ages ranged from 65 to 82 years (median 77 years). Nine were women and 6 were men. The time since glaucoma diagnosis was 7 months to 24 years (median 4 years). Eight of the 15 patients were included in the trial group (who participated in the compliance improving programme), 5 were included in the control group, and 2 were lost from the second recording period owing to defective monitor batteries. One of the latter was unable to participate in the interview.

Results

Monitor records from the 15 patients are shown in Figs. 1, 2, 3, and 4. All patients reported by interview that they were taking pilocarpine 3 times a day. Nine patients always administered the eye drops themselves. Four patients (nos. 3, 5, 6 and 7) were always and 2 (nos. 4 and 10) occasionally helped by some other person. At least 3 different ways of deviation from the 'ideal' medication behaviour can be identified.

(1) Inadequate spacing of doses during the day,

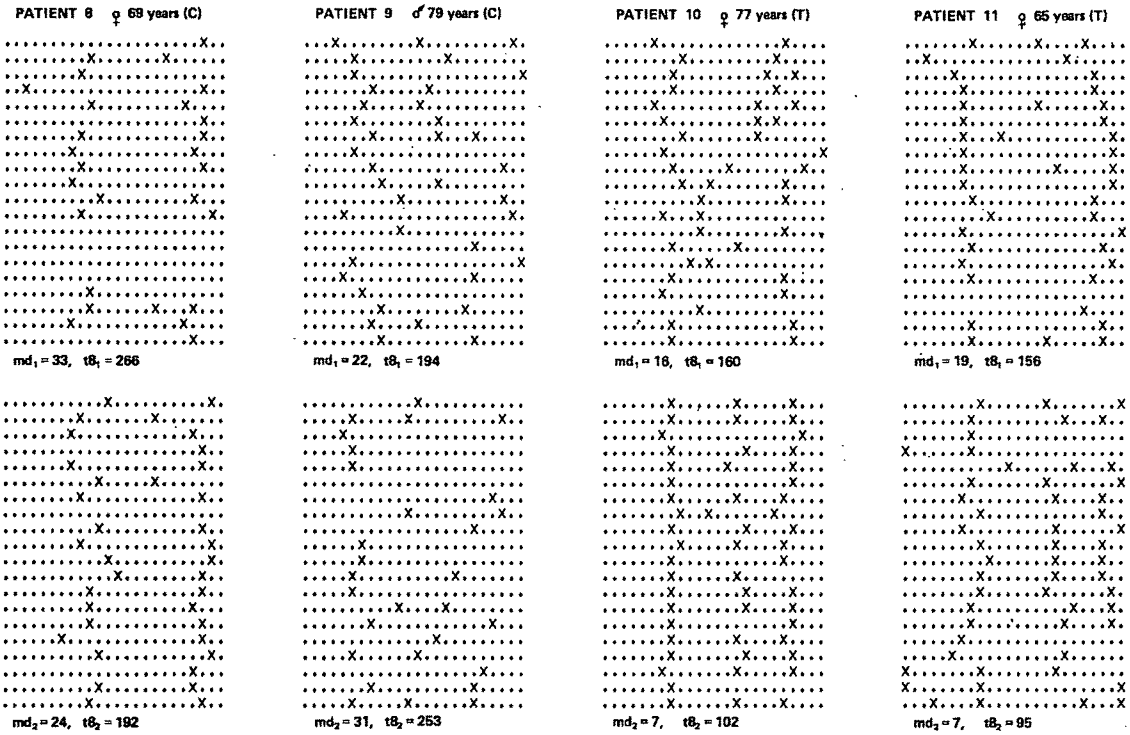

Fig. 3 *For legend see Fig. 2.*

with long intervals during the night. This is seen in the records for the first 20-day period from patients nos. 1–7 (Figs. 1 and 2). Most of these patients took almost all their doses during an 8-or 9-hour period in the day with a 15- or 16-hour interval during the night. Patient no. 5, taking most of her doses during 6 hours, concentrated her medication even more.

(2) Omitting the second (noon) dose. This pattern is seen in the first and second monitor records from patient no. 8 (Fig. 3). During the 40 days recorded this patient took pilocarpine as prescribed 3 times daily on only one day but used the eye drops twice a day on 26 days. Similarly, patients no. 4 (Fig. 1), nos. 9, 10, 11 (Fig. 3), and no. 12 (Fig. 4) missed the second dose on most days of their first monitor periods.

(3) Long interruptions in the medication were seen in 5 patients. As shown in the records from patients no. 2 (Fig. 1), no. 8 (Fig. 3), and nos. 13–15 (Fig. 4), these interruptions may last for several days.

The monitor record from patient no. 7 (Fig. 2) is an example of 'the medication behaviour' by the nursing staff of the long-term care clinic were he lived. In addition to inadequate time separation the doses were scattered, and a large number of doses were missed during the test period (11 out of 60 prescribed).

Most of the 8 patients included in the trial group, who participated in the education and tailoring programme, improved in their medication compliance during the second monitor period. For example, patients no. 3 (Fig. 1) and 5 (Fig. 2), who showed inadequate time spacing during the first monitor periods, separated their doses more evenly during the second periods. Patients 1 and 2 (Fig. 1) from the control group did not change their pattern of drug taking, however. Similarly, patients 10 and 11 (Fig. 3) from the trial group reduced the number of missed second doses, whereas control patients 8 and 9 (Fig. 3) did not. Patient no. 12 (Fig. 4), although she participated in the education and tailoring programme, did not show any improvement. According to her son this patient had a very poor memory. He called her several times during the day to remind her to take the eye drops. Patient no. 13 (Fig. 4) took almost all doses on the days before the clinic visit. He did not participate in the compliance improving programme and repeated his aberrant medication behaviour during the second monitor period. Patients 14 and 15 (Fig. 4) included in the trial

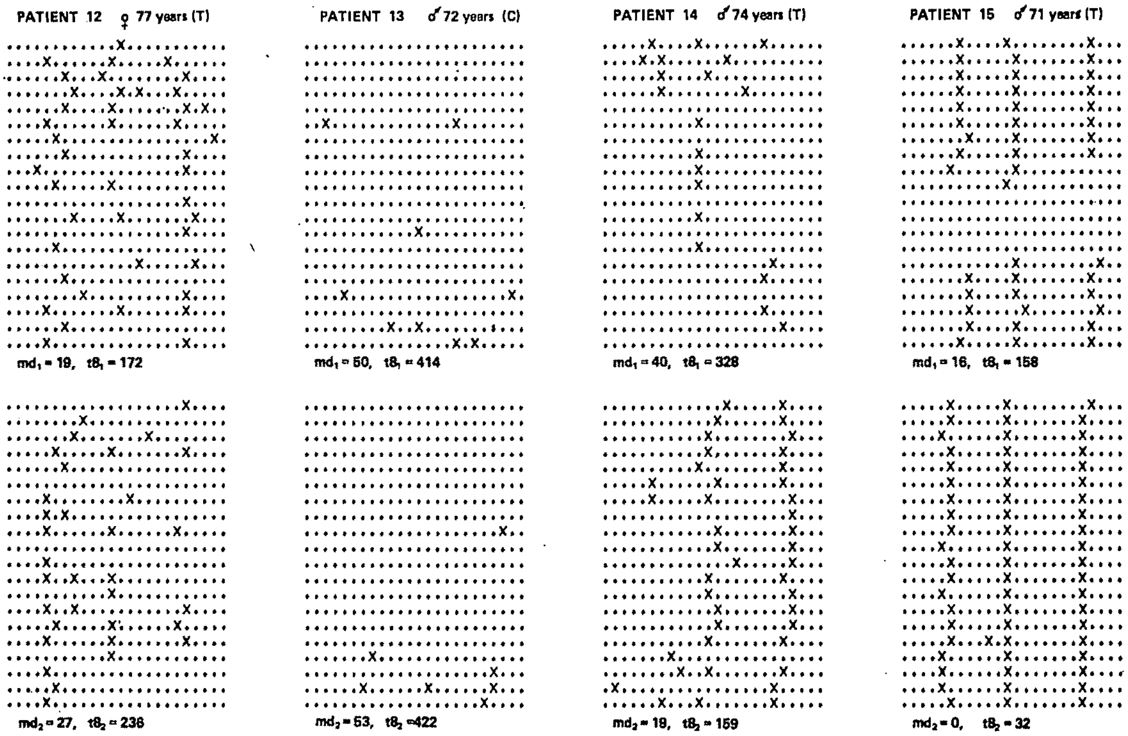

Fig. 4 *For legend see Fig. 2.*

group showed moderate improvement as their long dose intervals were reduced.

The IOP readings at clinic visits and the time span since the last dose of pilocarpine taken are shown in Table 1. On all but 5 of the 28 clinic visits the patients had taken the eye drops within 5 hours.

The number of missed doses reported by interview was inaccurately low (Table 2). Of 14 patients interviewed all but one reported that they had not missed a single dose during the past 7 days. Monitor data, however, showed that most of them missed several doses during the same period. Eleven patients reported spontaneous tailoring of doses to some special event in the morning (10 patients), during the middle of the day (6 patients), and in the evening (9 patients). The most frequently used events for tailoring were getting up in the morning, eating breakfast and supper, and going to bed.

Discussion

Some of the patients spacing their doses inadequately seemed to use the drug consistently 3 times a day at almost set times (e.g., patients 3 and 5). In that respect they may be termed compliant but seemed to be on a wrong medication schedule. The incorrect time spacing of doses may be due to inadequate or insufficient information to the patient about the interpretation of the prescription.[17] Without basic information on pharmacology the patient may not see any reason to separate the doses by equal intervals but may choose the hours of drug administration on some other basis. One patient, for instance, stated that it was easier to remember to take the eye drops if the times for medication were close together.

The second (noon) dose, the most frequently omitted,[18] seems to constitute a special problem for many patients. The results of the interviews indicate that many patients take their morning and evening doses close to some definite activity such as getting up and going to bed, but they seem to have difficulty in finding a convenient activity to which they can connect the noon dose. Misunderstanding of the number of daily doses prescribed might be another reason for frequently omitted doses. However, this could not apply to the patients in this study, as they all reported that they were taking pilocarpine 3 times a day.

The possible risks of the long dose intervals caused by inadequate time spacing and frequently omitted

Table 1 *Intraocular pressures (IOP) at the end of first (upper 2 figures) and the second (lower 2 figures) monitor periods, and the number of hours within which the last dose of pilocarpine was taken (monitor data).*

Patient number	*IOP*		*Last dose of pilo. within*
	OD	*OS*	
1	20	20	4 hours
	18	20	1 hour
2	—	—*	4 hours
	22	25	3 hours
3	16	24	2 hours
	14	26	4 hours
4	19	42	5 hours
	22	32	2 hours
5	12	16	3 hours
	16	18	3 hours
6	36	23	3 hours
	38	23	—†
7	11	12	4 hours
	8	6	—†
8	24	24	4 hours
	26	24	3 hours
9	33	44	5 hours
	36	36	4 hours
10	29	21	4 hours
	26	26	13 hours
11	20	21	8 hours
	18	18	3 hours
12	12	12	7 hours
	25	22	10 hours
13	19	22	1 hour
	18	20	4 hours
14	26	26	1 hour
	15	14	3 hours
15	13	13	4 hours
	16	18	14 hours

*IOPs not measured.
†Lost to the second monitor record.

second doses might seem obvious. However, the information on the duration of the IOP lowering effect of pilocarpine is contradictory. The most commonly accepted duration seems to be 6 or 8 hours,[19 20] but some data indicate that the effect may last for 12 or 13 hours,[21 22] and it may be difficult to predict the consequences.

Long interruptions in the medication may be the most serious type of noncompliance owing to the high proportion of the day without adequate treatment. In addition to the length of these interruptions their frequency will of course also determine their effect on the patient. For instance, patient no. 15 discontinued his medication when having radiotherapy for a tumour in the bladder. There is reason to believe that the break in his medication was exceptional.

Table 2 *Number of missed doses during the past 7 days according to interview and monitor, and reported spontaneous tailoring of doses to special events during the day. The letter in brackets indicates whether the patient was included in the trial group (T), in the control group (C), or was lost to the second monitor period (O).*

Patient number	*Number of missed doses during the past 7 days*		*Reported spontaneous tailoring of doses to special events*		
	interview	*monitor*	*morning*	*noon*	*evening*
1 (C)	0	3	+	+	+
2 (C)	0	8	−	−	−
3 (T)	0	0	−	−	−
4 (T)	0	2	−	−	−
5 (T)	0	1	+	+	+
6 (O)	0	—*	+	+	−
7 (O)	—†	—*	†		
8 (C)	0	8	+	+	−
9 (C)	0	8	+	−	+
10 (T)	0	3	+	−	+
11 (T)	0	3	+	−	+
12 (T)	0	8	+	−	+
13 (C)	4	15	+	+	+
14 (T)	0	6	+	−	+
15 (T)	0	0	−	+	+

*Lost to the second monitor record.
†No interview obtained.

Noncompliant patients with progressive visual field defects or unacceptably high IOPs might undergo needless changes to more potent drugs, with greater risks of severe side effects. A successful filtering operation may solve the problem in some patients. In others glaucoma surgery might be postponed if they show low intraocular pressures when taking the eye drops during the hours before clinic visits.

In clinical work the diurnal curve is sometimes observed to show lower IOP values than measurements in open care units. In these circumstances high IOPs on clinic visits might be assumed to indicate poor adherence to the drug regimen. This is not supported by our findings, however. Although noncompliant, the patients had taken a dose of pilocarpine within 5 hours before most of their clinic visits. Consequently the high IOP values recorded would probably not be due to their poor compliance (Table 1).

The inaccuracy of the interview as a measure of noncompliance (i.e., missed doses) in this study is in agreement with the findings of others.[16 23–25] However, interview may be valuable in determining the most frequently used times for medication.[26] Consequently, it may be worth trying to detect patients with inadequate spacing of doses in the clinical work simply by asking them about their times of medication.

The 15 patients of this study were the most noncompliant selected among 82. It might be argued that only a small proportion of the total number deviated seriously from the prescribed regimen. However, some data indicate that compliance will deteriorate with time,[18 27] and the monitor data collected between 2 clinic visits only 3 weeks apart will probably give too optimistic a view of the long-term compliance with medication. Furthermore, the patients studied represent 'survivors' at the clinic, and their compliance might be better than that of an inception cohort.[10]

To evaluate the clinical significance of noncompliance with pilocarpine therapy, long-term monitor studies should be done. There is also a great need for studies of the effect of different dosing of the drug on the progression of the glaucomatous process.

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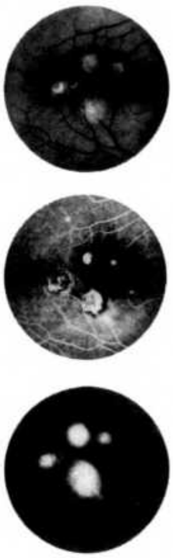

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LTI

British Journal of Ophthalmology, 1982, **66**, 471–473

Evaluation of laser iridectomy in angle-closure glaucoma: provocative tests

G. KARMON, T. VENDER, AND H. SAVIR

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SUMMARY An argon laser iridectomy was performed on 18 eyes of 14 patients with closed-angle glaucoma. The intraocular pressure (IOP) was controlled in all but one eye within normal limits. Variable amounts of pigment were found on gonioscopy in all cases. The mydriasis test was positive in one eye (5·5%) after homatropine and in 5 eyes (28%) after tropicamide drops. 80% of the positive results occurred in lightly pigmented irides. The dark-prone position test was positive in 7 eyes (38%), 71% of the positive results occurring in heavily pigmented irides. Tonography was also performed; the possibility of trabecular damage is discussed.

Since Meyer-Schwickerath's[1] first iridectomy with the use of a xenon arc photocoagulator other sources of radiant energy have been used, first the ruby laser operating at a wavelength of 694 nm,[2 3] and later on the continuous-wave argon laser operating at 488 and 515 nm, thus permitting the absorption of excessive heat by the circulating red blood cells. Khuri[4] working with rabbits and other workers[5–10] treating patients reported their experience in producing successful iridectomies.

Laser iridectomy is becoming increasingly popular as an alternative to surgical iridectomy. Various authors stress different aspects of the technique they used—for example, the amount of energy, the differences between the colour of the treated irides, etc. We report in this study the results of post-operative provocative tests in 18 eyes with successfully produced laser iridectomies.

Materials and methods

Eighteen eyes of 14 patients were examined (Table 1). These were consecutive cases of laser iridectomy treated by a continuous-wave coherent 900 argon laser adapted to a Zeiss slit-lamp biomicroscope.

The iridectomy was performed through a clear cornea without the use of a contact lens in a single-phase multiburn technique. The beam was aimed at the upper temporal or nasal quadrant 1 to 2 mm from the limbus. The coherent 900 continuous-wave argon laser settings used were 50 μm spot size, 0·1 second duration, and peak energies of 1500 to 2000 mW.

Table 1 *Details of patients in the study*

Number of patients	14
Number of eyes	18
Age range (mean 65·3 years)	41–78
Sex:	
male	5
female	9
Iris colour (eyes):	
light pigment (blue and hazel)	10
heavy pigment (brown)	8
Diagnosis (eyes):	
acute angle closure	1
chronic angle closure	17

Prior to the treatment miosis was achieved by instilling a few drops of 2% pilocarpine hydrochloride. At the end of the procedure dexamethasone-neomycin drops were instilled 6 times daily for 24 hours.

During the treatment a cloud of dispersed pigment and an air bubble originating from the posterior chamber were often observed. The procedure was considered successful when the anterior capsule of the lens was visualised through the iridectomy and positive transillumination was obtained.

One to 3 sessions were needed to obtain a patent

Correspondence to Dr G. Karmon, Department of Ophthalmology, Hasharon Hospital, Petah-Tiqva, Israel.

coloboma. In brown eyes a mean of 2·5 sessions was needed compared with 1·75 sessions in blue and hazel eyes. The number of burns needed to achieve the goal varied from patient to patient. It ranged from 54 to 280, but as a rule more burns were needed in heavily pigmented (mean 171·4) than in lightly pigmented irides (mean 128·0).

The patients were followed up monthly for 3 to 15 months, mean of 8·4 months. Gonioscopy was performed before and after the iridectomies. Kinetic perimetry (with a Haag-Streit Goldmann perimeter), cup-disc ratio determination, and tonography were done in all cases by the same person. In one patient (no. 10) tonography was performed before and after the procedure and the results were compared.

The mydriasis test was done several months after iridectomy, the intraocular pressure (IOP) being measured up to one hour after instillation of 2 drops of tropicamide 1%, and 1 week later when the test was repeated with homatropine 1%.

The dark-prone position test was performed as follows: the IOP was measured with a Goldmann applanation tonometer. The patient then lay face down on a nearby couch with his forehead resting on a pillow in a dark room. He was instructed to keep his eyes open and was observed from time to time to ascertain that he was alert and not asleep. After one hour the IOP was measured, the only source of light being the blue light of the Goldmann applanation tonometer. The measurements were repeated until the IOP returned to its original level.

Results

The argon laser produced a patent coloboma in all the eyes. Blue eyes were slightly more difficult to penetrate, and 3 blue eyes showed an incompletely penetrated anterior iris but a wide hole in the posterior iris with a clear retroillumination on biomicroscopy.

The IOP ranged from 11 to 20 mmHg in 17 eyes and 26 mmHg in one eye (patient no. 4) without medication.

Corneal opacities (epithelial and/or endothelial), when present immediately after treatment, disappeared within a few days. Small anterior focal lenticular opacities near the coloboma developed in 3 eyes, but they did not progress during the follow-up period.

On the day of treatment a low-grade iritis developed in all cases, but it subsided within 24 hours on a regimen of topical steroid drops 6 times daily. A slightly dragged pupil was observed in 5 eyes. Slight posterior synechiae were found in 5 eyes, but only in one eye (patient no. 1) with a blue iris were they extensive.

On gonioscopy pigment was found in all cases, extending from 4 to 7 o'clock in variable amounts. In 3 eyes a wide bridge of pigment spanning the angle was present. No pigment was found before the laser treatment in any of the eyes. An attempt to grade the amount of pigment in order to evaluate a possible difference between lightly and heavily pigmented irides showed no significant difference.

The results of the provocative tests are listed in Table 2. The dark-prone position test was positive (an IOP increase of 8 mmHg or more) in 7 eyes (38%); the mydriasis test was positive (an IOP increase of 8 mmHg or more) in one eye (5·5%) after homatropine drops and in 5 eyes (28%) after tropicamide drops.

Table 2 *Results of provocative tests*

Patient no.	*Eye*	*Iris colour**	*IOP increase in mmHg*		
			Mydriasis		*Dark-prone test*
			Tropicamide	*Homatropine*	
1	OD	L	2	0	0
2	OD	L	0	0	5
3	OS	B	8	3	3
4	OD	B	3	2	3
5	OD	B	3	2	8
6	OD	B	0	2	8
6	OS	B	0	2	10
7	OD	L	8	5	5
7	OS	L	9	6	5
8	OD	L	3	2	14
9	OS	B	6	0	14
10	OS	L	8	1	6
11	OD	L	4	2	3
11	OS	L	4	2	4
12	OD	B	2	9	13
13	OS	B	5	1	0
14	OD	L	4	0	8
14	OS	L	8	1	1

*L=lightly pigmented iris. B=brown iris.

The positive results of the provocative tests in the lightly and heavily pigmented irides (Table 3) showed that a positive result after tropicamide occurred in 4 lightly pigmented irides, whereas the dark-prone position test was positive in 5 heavily pigmented irides.

Tonography revealed that in 16 of 18 eyes there was evidence of a decreased trabecular outflow after laser iridectomy. Pretreatment data were available in only one eye (patient no. 10), the patient being on a regimen of pilocarpine 2% 3 times daily (Table 4). The tonography was repeated in the untreated eye as well, the results being similar to those obtained earlier (C=0·24; Becker index=100).

Fundus examination was performed and showed no retinal damage in any case. Fluorescein angiographic and static perimetry studies were also done, and the results will be published later.

Table 3 *Positive provocative tests according to iris colour*

	IOP increase of 8 mmHg or more		
	Mydriasis test		*Dark-prone test*
	Tropicamide	*Homatropine*	
Heavily pigmented iris	1	1*	5
Lightly pigmented iris	4	0	2
Total	5	1	7

*This eye responded positively also to the dark-prone test (OD in patient no. 12).

Table 4 *Results of tonography in one eye of patient no. 10*

Specification	*C*	*Becker index*
Before laser iridectomy*	0·25	100
After laser iridectomy	0·07	190

*On pilocarpine treatment.

Discussion

The advantages of the argon laser over the surgical method in producing a patent coloboma are obvious and have been discussed.[8,9] In all but one eye this treatment successfully controlled the IOP without the need for additional medication. The purpose of the various provocative tests is to assess the likelihood of the IOP's increasing in the future. We found a positive dark-prone test in 38% of the eyes compared with 22% in a surgical peripheral iridectomy study performed in our department (submitted for publication) and 60% reported.[11]

The mydriasis test after homatropine was positive in only one eye (5·5%) as compared with 20% in our surgical iridectomy study. The mydriasis test after tropicamide was positive in 28% of the eyes. Yassur *et al.*[9] found a negative test in all but one eye of their series, yet they did not perform this test in their third group of eyes (chronic closed-angle glaucoma).

The difference between the occurrence of positive tests in the lightly and heavily pigmented irides is difficult to explain. It is known that mydriatics are less effective in dark eyes than in light ones[12]; thus the dilating effect of 2 drops of tropicamide on the individual pupil varied according to the iris colour.

The explanation for the higher percentage of positive dark-prone test results in eyes with heavily pigmented irides is speculative. The anterior displacement of the lens during the test is not influenced by the iris colour. Therefore the difference between the response of the eyes with heavily and lightly pigmented irides to the dark-prone test must lie in the pupil's diameter and/or the amount of pigment in the angle. The visual evaluation of the amount of dispersed pigment seen on gonioscopy is inaccurate. It is possible that pupils with heavily pigmented irides dilate to a less extent in darkness than pupils with lightly pigmented irides. Thus a pupillary block mechanism might more readily occur in the mid-dilated pupil.

The tonographic results seem to indicate the possibility of trabecular damage by the dispersed pigment following iridectomy. The normal tonographic results in the fellow eyes in cases with monocular laser iridectomy are not comparable, since all eyes were under treatment with pilocarpine, which influences the outflow facility. In our study group the majority of patients had chronic angle-closure glaucoma with trabecular damage, and therefore the discontinuation of pilocarpine treatment after iridectomy reduced the damage though the IOP was controlled. This explains also the change in the tonography results in patient no. 10 (Table 4). Further studies are needed to compare tonographic results after laser iridectomy in patients with angle-closure glaucoma when the tonography before the procedure gives normal findings and the patient is kept on a regimen of pilocarpine after the procedure until the tonography is performed.

The possibility of retinal damage following laser iridectomy cannot be excluded.[6,8] Fundus examination is not sufficient; static perimetry and fluorescein angiography are needed to evaluate this possibility, and our results are being prepared for publication.

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British Journal of Ophthalmology, 1982, **66,** 474

Correspondence

Quantitative trabeculectomy

Sɪʀ, I read with great interest the article[1] by Drs. Robert David and Uriel Sachs. I presented a similar paper before the All India Ophthalmological Society in January 1980. This paper which is to be published in the *Proceedings of the All India Ophthalmic Society,* is entitled 'Control of filtering bleb in trabeculectomy.'

My paper essentially reports a direct relationship between scleral flap thickness and resulting intraocular pressure. This conclusion was based on clinical studies concerning 3 groups of patients who had undergone trabeculectomy (54 eyes of 42 patients) with varying thicknesses of scleral flaps. In groups I and II the scleral flaps consisted of 2/3 and 1/2 thickness respectively, and in group III the scleral flap was 1/3 thickness.

There was evidence of subconjunctival drainage in 95% of the eyes. In 77% trabeculectomy alone achieved the desired levels of intraocular pressure and 20% of eyes needed additional pressure-lowering medication. One eye had to be reoperated on. In group III the bleb was more obvious, and postoperative intraocular pressure was between 9 and 13 mmHg. In groups I and II the blebs were less obvious and intraocular pressures were between 14 and 18 mmHg.

My study suggests that, by altering the thickness of scleral flap during the trabeculectomy operation, one can achieve the desired level of intraocular pressure in most cases. A thin scleral flap was advised in patients with extensive glaucomatous damage.

I would also like to point out that H. Saul Sugar should be recognised for his pioneering work in this area. He was the first to describe this subject in 1961.[2]

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Sɪʀ, In their recent paper David and Sachs[1] suggest that adjusting the thickness of sclerocorneal tissue excised at trabeculectomy allows graded reduction in the intraocular pressure. They do not, however, offer any control operations for comparison, and they have overlooked recent evidence that a standard ungraduated trabeculectomy operation reduces the intraocular pressure to the physiological range irrespective of the preoperative pressure.[2] It therefore seems that the pressure control is not related to the graduated dissection, and this proposed modification introduces a spurious and unnecessary complexity.

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Sɪʀ, Our paper, entitled 'Quantitative trabeculectomy.' deals with a surgical technique, while Jay and Murray's publication deals with intraocular pressure (IOP) reduction. There seems to be no major contradiction between our results, the question remaining whether the operating technique used on the 98 eyes in their series was identical. This is unlikely, as the procedure was performed by several members of the surgical staff, both juniors and seniors. As quantitative trabeculectomy is performed under high magnification, it is not unlikely that a certain amount of variation in the thickness of the sclerocorneal tissue removed did occur in their series too.

In 11 of our cases the preoperative IOP was more than 40 mmHg, and an average reduction in IOP at the 16-20 mmHg range as found by Jay and Murray should have been unsatisfactory. A higher reduction was obtained in these patients by removing 4/5th of the corneoscleral tissue thickness.

We disagree with the suggestion that 'control operations for comparison' should be performed. These would aim for improper reduction in the IOP, which of course is medically unjustifiable.

ROBERT DAVID
Soroka Medical Center,
Beer-Sheba,
Israel.

Obituary

Air Marshal Sir Philip Clermont Livingston, KBE, CB, AFC, FRCS

Air Marshal Sir Philip Clermont Livingston, known to all his friends as P.C., died on 13 February 1982 at his home in Canada at the age of 88. He was an outstanding individual—not only because of his splendid physique but because he was endowed with a personality that was at once individual, attractive, kind, sympathetic, and above all enthusiastic.

Born in Vancouver on 2 March 1893 of British parents, he came to the UK on the death of his father and became an undergraduate at Jesus College, Cambridge, where in 1914 he gained a rowing blue. He rowed number 3 in the winning Cambridge University crew in March 1914. After passing his second MB he joined the RNVR, and from 1914 to 1917 served as a surgeon-probationer on torpedo boat destroyers and armoured cruisers.

After qualifying at the London Hospital he elected in May 1919 to join the Medical Branch of the then embryonic Royal Air Force and proceeded, with foresight, to take the diploma of public health followed by qualifications in ophthalmic medicine and surgery and the FRCS of Edinburgh. He was later elected a Fellow of the Royal College of Surgeons of England.

In 1929 he was posted to Iraq as General Surgeon in the RAF, and while there he gained wide experience at the Royal Baghdad Eye Hospital, at the same time learning to fly and gaining his Wings. He then began to study the effect of sunglare on flying personnel in Iraq.

In 1934 he was appointed consultant in ophthalmology and he remained consultant until 1947. In 1937 he made a tour of medical establishments in Germany used for the selection of future German air force pilots. It was as a result of this visit that the then inferior flying equipment of the RAF was redesigned, and apparatus for evaluating the physiological needs of pilot and air crew was constructed. The 22-ft long low-pressure chamber, the human centrifuge, the depth perception and night vision apparatus, and the redesign of an RAF goggle are some examples of his drive and foresight.

He regularly attended the Congresses of the Ophthalmological Society of the United Kingdom and gave some interesting papers, including 'Heterophoria in aviation, its significance and treatment' in 1941 and 'Ocular disturbances associated with malnutrition' in 1948.

All this is admirably summed up in an appreciation which appeared in *The Aeroplane*:

> 'Livingston, who was a Specialist in Ophthalmology to the R.A.F. during the War, perhaps because of his personal experience of a pilot's needs, was better able than most specialists to appreciate the limitations of the consulting room. His deep knowledge of human nature, coupled with his ophthalmic skill and long acquaintance with aviation, allowed him in passing men for flying duties in the R.A.F. to offset optical infirmities by flying experience and courage. Many pilots, well below the accepted standards of vision, owe their successful flying careers to Sir Philip's perspicacity.'

He was appointed Deputy Director General of the Medical Services (RAF) in 1947 and was promoted to the post of Director General one year later. He held this appointment until he retired in 1951. His honours and awards included the OBE in 1938, the AFC in 1942, the CBE in 1946 and in the same year also the Medal of Merit (Czechoslovakia), the CB in 1948, and the KBE in 1950. He was honorary surgeon to the King from 1948 to 1950 and was a Commander of the Order of St John. He won the Chadwick Prize and Gold Medal for research and he gave the Montgomery, Moynihan, and Chadwick lectures in 1942–5. On retirement he returned to Vancouver Island, where he continued to practise ophthalmology and where he wrote an interesting autobiography entitled *Fringe of the Clouds* (1962).

He was married in 1920 to Lorna Muriel, only daughter of C. W. Legassicke Crispin, of London. He is survived by his widow and one of his 2 sons.

T. KEITH LYLE

Dorothy R. Campbell, MA, MB, BS, FRCS, DOMS

The death of Mrs Dorothy R. Campbell on 12 March 1982 will be mourned by many ophthalmologists who regarded her as a colleague and friend. She was in her eightieth year.

Dorothy Rose Adams was born in St Albans, Herts, on 12 April 1902. She gained an entrance exhibition to Girton College, Cambridge, in 1920 and proceeded to first-class honours in the natural sciences tripos, acquiring several prizes on the way. These included a scientific and industrial research studentship for research on the crystalline lens for the Glassblowers Cataract Committee of the Royal Society. Her medical studies were continued at University College Hospital, London, from whence she graduated in 1926.

From 1927 to 1930 she was first a clinical assistant and then a house surgeon at the Central London Ophthalmic Hospital—more recognisable to many under its later name of the Institute of Ophthalmology, Judd Street. She married Dr George Campbell in 1931, and while he maintained a busy general practice in the area she became ophthalmic surgeon to the Hospital of St Cross, Rugby, in the same year. She was also outpatient officer at the Birmingham and Midland Eye Hospital and in 1934 until 1940 was assistant surgeon there.

Mrs Campbell relinquished her post at Rugby in 1937 and joined the consultant staff of the Coventry and Warwickshire Hospital, remaining there until her retirement in 1962. From 1945 until 1965 she was director of the research department at the Birmingham and Midland Eye Hospital and was well known for her research into miner's nystagmus, migraine, and vitamin A metabolism in retinitis pigmentosa. She was a keen biochemist and maintained an interest in the metabolism of the retina until her last illness.

She was also an ardent supporter of women in medicine and the allied professions and had a close association with the orthoptists, starting the orthoptic school in Coventry and being a member of and an examiner for the British Orthoptic Board. She also examined in the diploma in ophthalmic medicine and surgery and was at various times vice-president of the Ophthalmological Society of the United Kingdom, president of the Midland Ophthalmological Society, and deputy master of the Oxford Ophthalmological Congress. In 1954 she was elected FRCS and in 1979 was made the first honorary member of the emeritus section of the International Association for Eye Research, of which she had been a founder member when, under the patronage of Sir John Parsons, it was known as the Eyeball Club.

Her enthusiasm for her work did not prevent Mrs Campbell from enjoying a close family life and an enthusiasm for sailing, which she shared with her husband, spending most of their spare time on the water at Burnham-on-Crouch.

Her husband survived her death by only 3 weeks and they leave one son, one daughter, and 2 grandchildren.

M. HANDSCOMBE

Notes

Diabetic retinopathy

The Wilmer Institute of the Johns Hopkins Hospital will present a conference entitled 'Diabetic retinopathy—1982' on 24 September 1982 in Baltimore, Maryland. The conference will review the current knowledge of the epidemiology, diagnosis, photocoagulation treatment, and prognosis of patients with all stages of diabetic retinopathy. For further information, contact: Program Coordinator, Office of Continuing Education, The Johns Hopkins University, 720 Rutland Avenue, Turner 22, Baltimore, Maryland 21205, USA.

Fifth International Orthoptic Congress

The Fifth International Orthoptic Congress will be held in Cannes, France, on 11–13 October 1983. The official languages will be English, French, and German, with simultaneous translation. Those wishing to offer papers, films, or posters should apply to the Secretary, International Orthoptic Association, Moorfields Eye Hospital, High Holborn, London WC1V 7AN, for the relevant forms (stating preferred language—English, French, or German). These forms must be completed and returned not later than 30 September 1982. All other information from Michele Marsot, General Secretary, Vth International Orthoptic Congress, 119 Cours Gambetta, 69003, Lyon, France.

Intraocular Implantlens Council

The first congress of the European Intraocular Implantlens Council will be held at The Hague, The Netherlands, on 30 September to 2 October 1982. Details from the Secretariat of the 1st EIIC Congress, c/o Holland Organising Centre, 16 Lange Voorhout, 2514 EE The Hague, The Netherlands.

Jules François Prize

The next Jules François Prize will be awarded in December 1983 and is valued at 200 000 Belgian francs. This triannual presentation will be made to the candidate whose work has made the most significant contribution to ophthalmology. Applicants must not be over 40 years of age on 1 January 1983. Interested parties may apply either themselves or through a third party to the Secretary of the Foundation, Dr Jean D'Haenens, E. Beenaertstraat 34, B-8400 Ostend, Belgium. Applications must be accompanied by supporting typewritten documents either in the form of a 10 to 15 page copy of the original work or a collection of papers supporting the work. Applications must reach the Secretary not later than 31 December 1982.

Ultrasonography

A course on ultrasonography of the eye and orbit will be held on 11–16 October 1982 at Würzburg. The language of the course is German. Details from Professor Dr W. Buschmann, Univ.-Augenklinik, Josef-Schneider Strasse 11, D-8700 Würzburg, Germany.

British Ophthalmic Instrument Design Award

A British Ophthalmic Instrument Design Award has been established by the joint action of the Faculty of Ophthalmologists, the Ophthalmological Society of the United Kingdom, the Oxford Ophthalmological Congress, and the Ophthalmic Section of the Royal Society of Medicine. In the first instance any design which has been developed and marketed within the last 5 years will be eligible for the award. Applications (10 copies) should be sent to Miss M. M. Hallendorff, Faculty of Ophthalmologists, Royal College of Surgeons, 35/43 Lincoln's Inn Fields, London WC2A 3PN. They should include a full description of the instrument design, development, and manufacture together with the role which the distributor expects the instrument to play in British ophthalmic practice. A firm assurance must be given that: (i) the original design or innovation was formulated by a person normally resident in the United Kingdom; (ii) the manufacture is wholly or in major part undertaken in the United Kingdom; (iii) the device/design is being promoted and distributed in the United Kingdom by a British based company. The closing date for applications is 30 November 1982. Applications will be considered in February of the following year. The award will take the form of a certificate which will be awarded to the distributor of the instrument. The winner of the award may use a reproduction of the award logo on stationery and in future advertisements. For further details contact Miss M. M. Hallendorff.

Current concepts course

The Wilmer Institute of the Johns Hopkins Hospital will present the Fifth Annual Current Concepts in Ophthalmology course, 27 February–6 March 1983, at the Cerromar Beach Hotel, Dorado Beach, Puerto Rico. The course will cover topics in anterior segment diseases and cataract surgery as well as posterior segment disorders and ultrasound. Registration Fee: $425. Further information from Program Coordinator, Office of Continuing Education, The Johns Hopkins Medical Institutions, 720 Rutland Avenue, Turner 22, Baltimore, Maryland 21205, USA.

Facial surgery congress

The Interspecialty Facial Surgery Congress for Aesthetic Cancer and Reconstructive Surgery will be held on 27–30 April 1983 at the Waldorf-Astoria, New York, under the aegis of the International Oculoplastic Society. Details from IFSC Secretary, c/o Pierre Guibor, MD, 630 Park Avenue, New York, NY 10021, USA.

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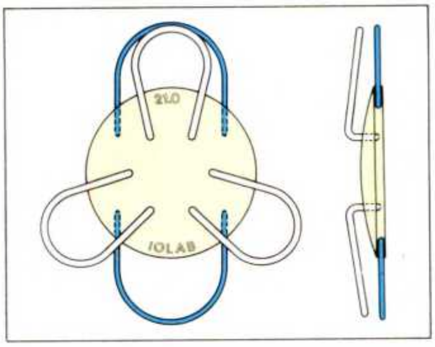

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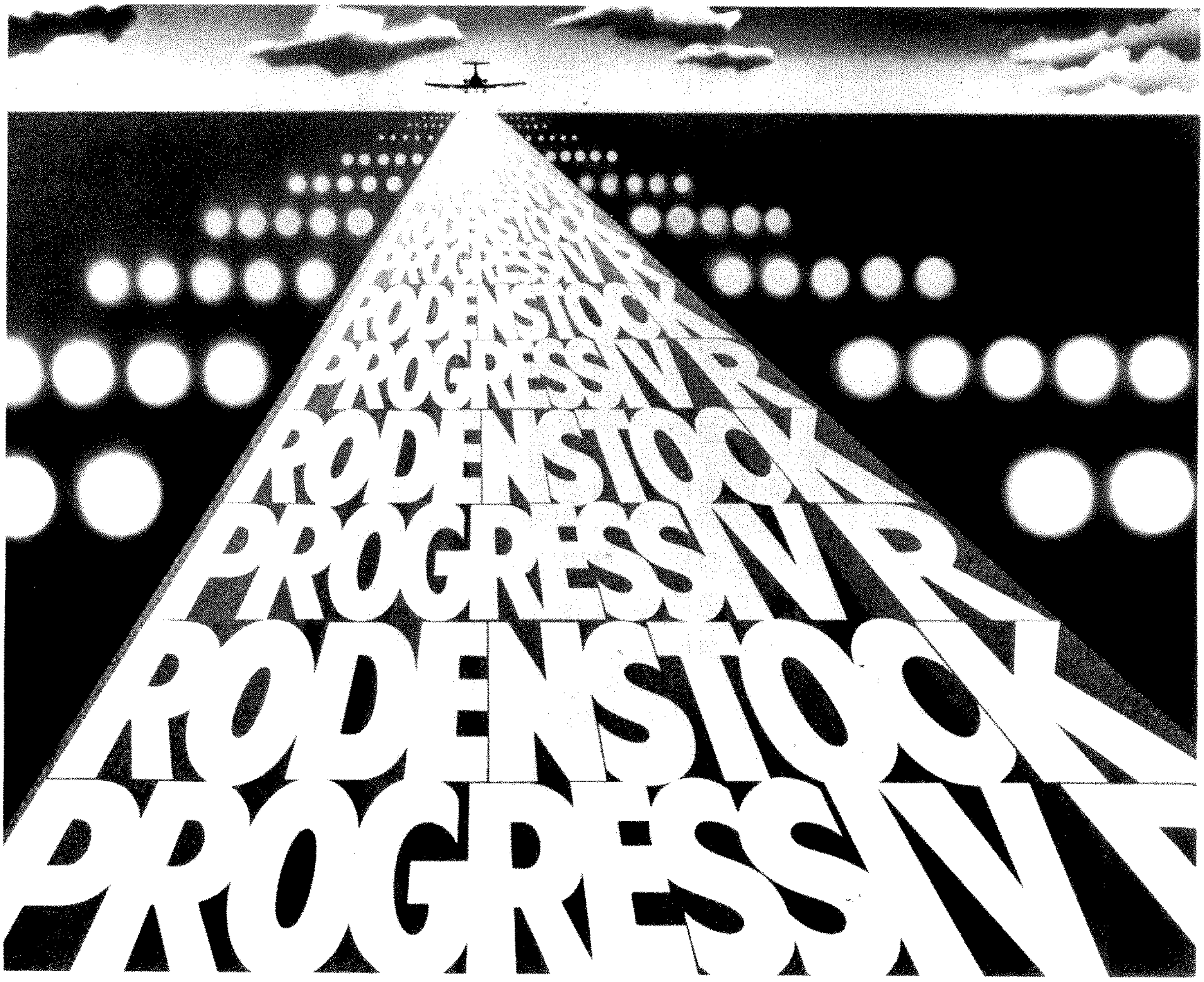

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ASTM CODEN BJOPAL 66 (7) 405-476 (1982) ISSN 0007-1161

British Medical Association Tavistock Square London WC1H 9JR

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August 1982 Vol. 66 No. 8

British Journal of
Ophthalmology

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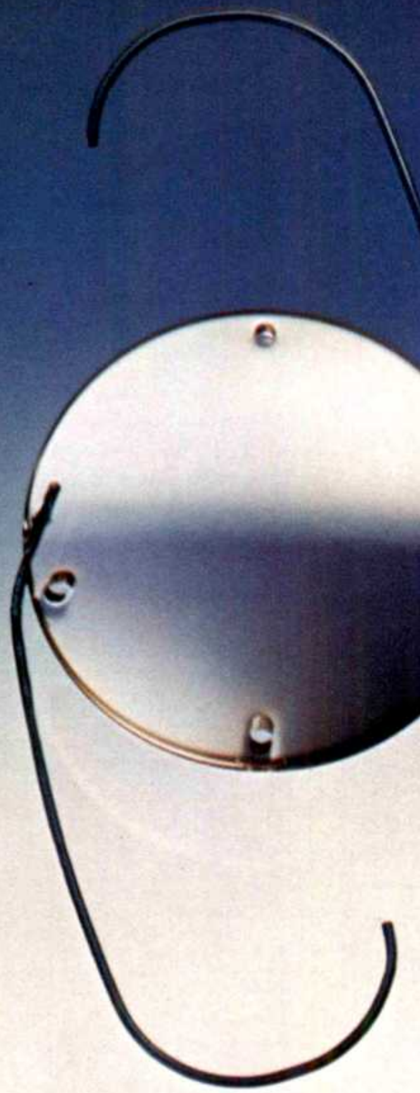

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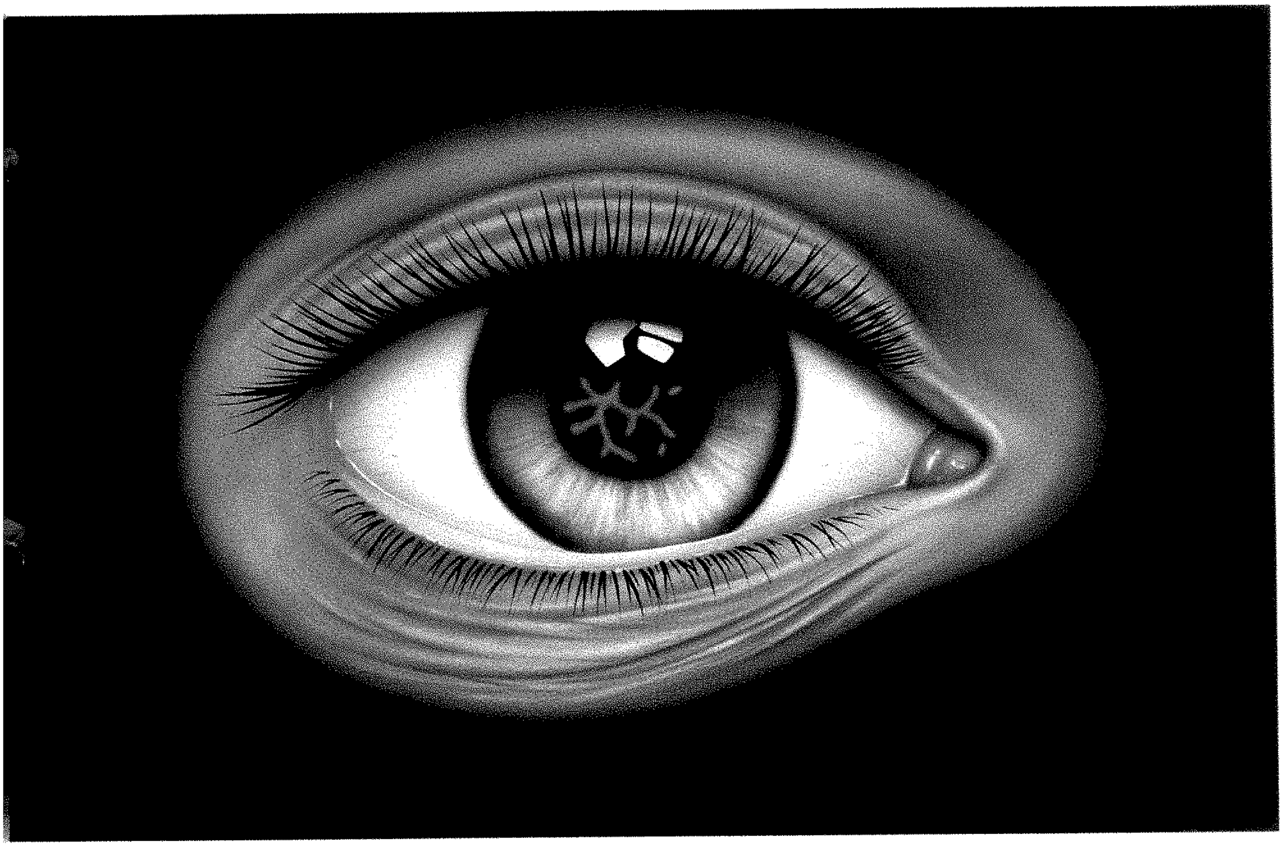

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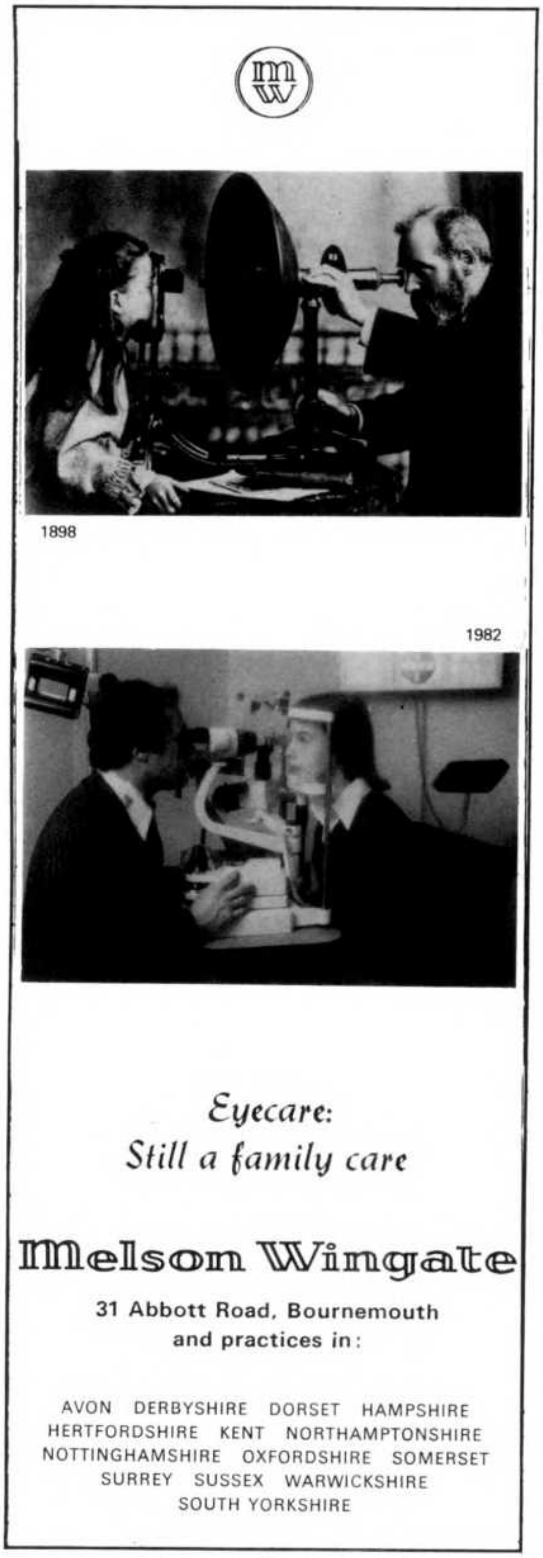

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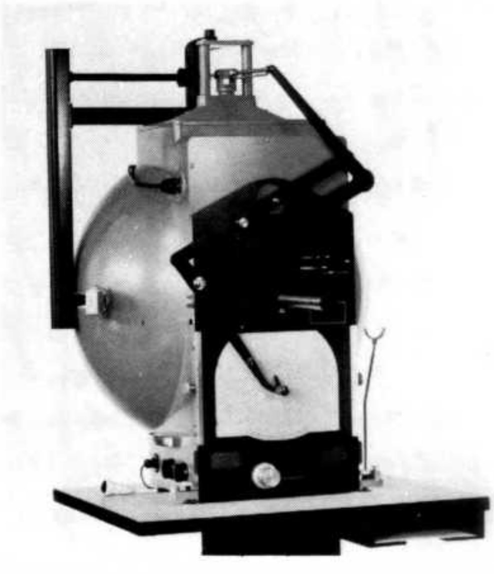

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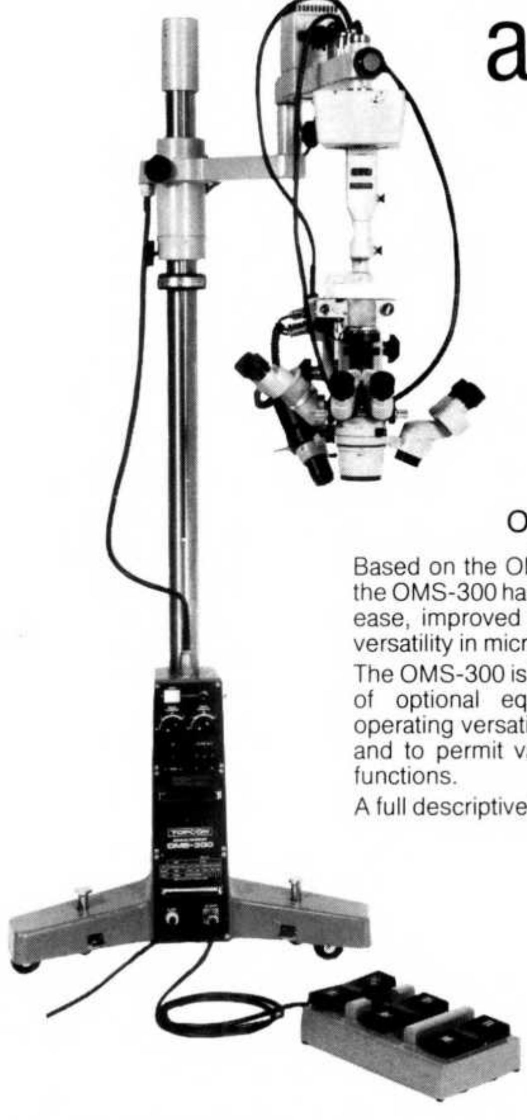

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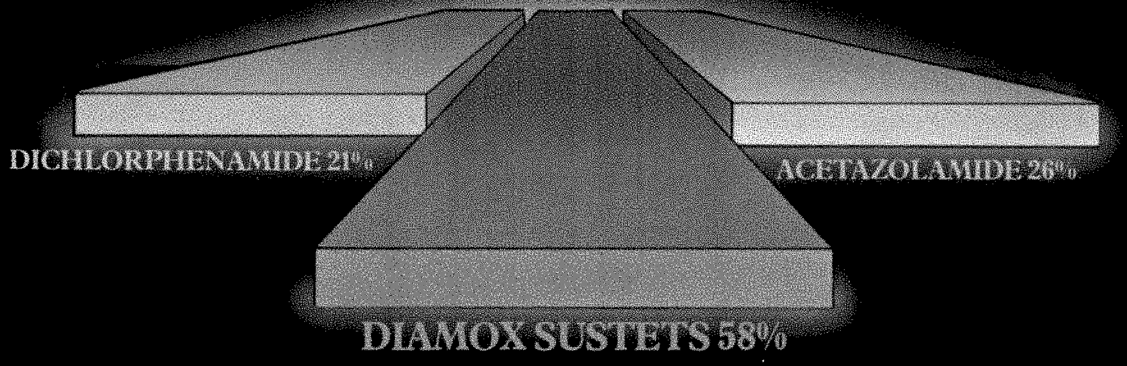

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British Journal of Ophthalmology, 1982, **66**, 477–491

A forced-choice test improves clinical contrast sensitivity testing

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SUMMARY Decreased contrast sensitivity has been demonstrated in early glaucoma, but the deficit is not regularly observed. We designed a prototype for a forced-choice printed test and evaluated it with several other measures of contrast sensitivity. The results also bear on the pattern of loss and the variables which effect performance. Mildly glaucomatous patients show a 6 db (50%) loss of contrast sensitivity at all spatial frequencies tested compared with age matched controls. Moving gratings give the same information as stationary ones, and practice effects are negligible. Contrast sensitivity at or below 2 cycles/degree is poorly correlated with visual acuity and does not change with age in the forced-choice test. Subjective judgment made the apparent contrast threshold higher, age dependent, and more variable, particularly at higher spatial frequencies. The pattern of variability can explain some reports of insignificant effects and why low spatial frequency contrast sensitivity detects glaucoma better than visual acuity. Methods correlated so poorly, despite high reliabilities, that uncontrolled biases must be suspected in subjective measures. Our new forced-choice format was superior to all other tests on at least one formal criterion and always at least equal to them. Improvements in contrast sensitivity screening tests are thus indicated.

There are several recent reports that printed tests of low spatial frequency contrast sensitivity are a sensitive, quick, and clinically convenient indicator of early glaucoma[1–6] and other eye diseases.[2 7 8] Some studies have obtained significant results only over a limited range of spatial frequencies,[2] test conditions,[4 9–11] or subject ages.[8 12–14] Arden[2] believed that low spatial frequency losses were the most direct index of peripheral retinal damage. In his test greater deficits occur at higher spatial frequencies (3·2 and 6·4 cycles/deg), where similar losses can be caused by aging and other optical factors.[11–15] If loss of spatial frequency contrast sensitivity in disease was mainly a consequence of these factors, there would be no clinical advantages in measuring it. The known biases occur in studies which use the rapid but subjective method of adjustment. Forced-choice measures, which are essential to minimise methodological biases,[16–19] have never been employed.

We devised a simple, rapid, printed, contrast sensitivity test with a psychophysically precise 4-alternative forced choice (4AFC) format. We compared it to an oscilloscope display of gratings, either stationary or phase reversing, and the original printed test[1 2] with groups of various ages, including glaucoma patients and age matched elderly normal persons. Our chief purpose was to compare the tests. There are methods specifically designed for this purpose. Normally the same population is tested at least twice with each of the tests to be compared. There will normally be a group which the test aims to discriminate. They should be tested and their scores compared with those of normal control groups. It is then possible to say which is the better test in terms of a number of comparisons between the several retests or groups. These are measures of:

(1) *reliability*—ordering should change as little as possible on retest (i.e., the correlation of test and retest should approach 1·0); (2) *stability*—absolute scores should change as little as possible on retest (i.e., the difference between the mean scores of test and retest should approach 0·0); (3) *generality*—the mean and standard deviation should not change with social variables, for example, age, socioeconomic

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group or level of co-operation; (4) *efficiency*—the separation of the target group (in this case individuals needing clinical attention) from the rest of the population should be as great as possible; (5) *utility*—the test should be fast and easy to use without sacrificing efficiency.

Our new test always equalled the others and surpassed each of them on at least one of the 5 criteria. By comparing the 4 methods we got additional insight as to why and when contrast sensitivity testing can be of value. A brief report of this research has been published previously.[16]

Methods

Visual acuities were always tested with printed test charts illuminated to a constant level by bright overhead fluorescent lights. Far visual acuity was determined with a Snellen chart at 6 m and near visual acuity with a Sheridan-Gardiner single letter series at 30 cm. Subjects wore their appropriate optical correction for each distance. Visual acuity was converted to a ratio which included the proportion of errors on the last visible line, so that small variations could influence the analysis.

We had 3 methods of displaying sinusoidal gratings and a different testing method was required for each one.

(1) *Arden's printed test.* This test consists of a series of 5 plates with printed reproductions of swept contrast gratings.[12] (Contrast here signifies the dimensionless ratio $(L_{max}-L_{min})/(L_{max}+L_{min})$ where L_{max} and L_{min} are the luminances of the brightest and darkest points in the stimulus respectively.) The page edge is marked with a scale, each unit of which is equal to a contrast change of 0·08 log units (1·6 db). The scale is placed arbitrarily and runs from 0, which is below normal threshold, to 20, which can be easily seen by most visually normal people. Successive plates are separated in spatial frequency by octave steps (doubling of frequency), starting at 0·2 cycles/cm and progressing to 6·4 cycles/cm. The 2 highest spatial frequencies are printed on each half of the final plate. The tester first familiarises the subject with the stimulus and then covers it with a grey card of approximately the same reflectance. The card is pulled up the sheet exposing the lowest contrast first, at the rate of about 1 unit/s, until the subject reports he can see the stripes. The number at the margin is recorded. The test takes about 5 min to administer.

We used the exact procedure specified with the test instructions with 3 exceptions. Firstly, lighting was by the overhead fluorescent lights of the clinic supplemented by that from a nearby window and not by a desk lamp directly above, since we found that there was less diffuse reflection from the page (glare) and that we obtained the same result without the additional illumination. Secondly, the test distance was 28·5 cm and not 57 cm, since this was closer to the patients' reading distance. The spatial frequencies studied thus range from 0·1 to 3·2 cycles/deg. Finally, observers who failed to detect any grating were given a nominal score of 21 for the purpose of analysis, rather than 25, since a group of scores so distinct from the rest would have skewed the distribution of scores in some groups and thus increased variance excessively.

(2) *The 4-alternative forced-choice (4AFC) test.* The Arden plates were cut into a series of discs. Each disc differed from the next by one scale unit (see above). Disc diameter was 7 cm for plates 2 to 5 (0·2 to 1·6 cycles/cm), which therefore varied from scale level 3 to 17 and 3 cm for plates 6 and 7 (3·2 and 6·4 cycles/cm), covering levels 2 to 19. With these sizes contrast varied little within a plate, and there were enough grating cycles on the disc (except that there were only 2 cycles for the coarsest grating). Each series was mounted on a grey card of similar mean reflectance, high contrasts first. Because the sweep direction defines a top there are 8 orientations differing from vertical in steps of 45 degrees. Each was used once in random order before the set was repeated. The subjects were aware of only 4 possible orientations—horizontal, vertical, and left and right oblique—which they had to identify.

We used precisely the same viewing conditions for the 4AFC and Arden tests. In demonstration and practice trials the tester described the 4 possible answers then asked the subject to tell him which way the stripes ran on the highest contrast disc at a moderate spatial frequency, where most people are most sensitive. Children as young as 3 years of age could follow the stripes with their finger and thus demonstrate adequate co-operation. Older people used a combination of naming and pointing. On test trials the various spatial frequencies were always presented in either an arbitrary or prearranged random order depending on the particular study. Observers worked down through the contrast scale until they made an error. A second guess was always elicited, because it was unlikely to be correct by chance alone ($p=1/3$). The threshold was taken as the disc preceding that on which the observer made 2 errors. Testing time was about twice as long as the Arden test (i.e., 10 min) but could be much longer with some uncooperative children.

The 4AFC test design improvement relies on its great formal similarity to clinically established visual acuity tests like the Sheridan-Gardiner, Snellen, Illiterate E, and Sjögren hand. There are several distinct responses and the tester always knows, from an answer sheet if need be, whether answers are right or wrong. Previously described clinical tests of contrast sensitivity have never incorporated objective scoring, even when utilising oscilloscope displays under computer control. Certainly no previous printed test[1 2 20] has these features. (Atkinson *et al.*[21] have recently reported one such test. It was being developed at the same time as ours but has a purely research-orientated format and application.)

(3) *Oscilloscope with manual contrast control.* Gratings were generated directly on the face of a Telequipment D83 oscilloscope by the television technique of Schade[22] as modified by Robson.[15] When phase reversing and standing gratings were compared, the pattern was determined by a microprocessor controlled grating generator.[23] Subjects could set the contrast with a potentiometer placed near their right hand. Equal increments of rotation produced equal increments of log contrast over a range of 2 log units (40 db). Contrast could be read directly in db from a digital voltmeter, visible only to the tester. Additional fixed attenuation of 10 or 20 db was often used when the more sensitive young subjects were tested. Spatial frequency could be read directly from a meter and was continuously adjustable. The subject sat with his or her chin on a chin rest, which ensured the eyes were positioned 28·5 cm from the display. The screen subtended 26×20 degrees at the eye and was approximately 100 candelas/m^2 in luminous emittance. Frame rate was 100 Hz. Contrast of the screen was within the linear range for the spatial frequencies used, which were always below 12 cycles/deg. After the first experiment the distance and spatial frequencies used were the same as those for the printed tests.

The test was described and demonstrated to the subjects, who were then given some practice at controlling contrast. On each trial a new spatial frequency was selected. Subjects were asked to turn the contrast rapidly towards maximum and to turn it down again as soon as they had seen the stripes clearly. They then turned the contrast up smoothly, slowly, and evenly until the stripes first appeared. It was explained that at this point the pattern would be difficult to see and might come and go. (It should be noted that we did not determine a descending contrast threshold. In common with other laboratories (R. Hess, personal communication) we find that descending settings are much more variable. Many subjects cannot decide when the grating has finally disappeared and, even with a logarithmic contrast control, will turn it to the maximum excursion, far below any likely threshold. These errors increase with rate of change.) We did not permit the subject to make any further contrast adjustments (bracketing). The tester watched the meter to ensure that the rate of contrast change was always about 0·5 db/s and corrected the subjects if they turned the contrast knob too rapidly. Each of the 6 or 7 stimuli used in the experiment was presented once in random order. The set was then repeated. There were 4 sets in experiment 1 and 5 in experiment 2. Each set took about 10 min to complete and instruction a further 10.

Subjects

Subjects were volunteers from the patients and staff of New Addenbrooke's Hospital, Cambridge. Glaucomatous subjects were patients at the Eye Clinic. Most normal observers, including the unrelated, age matched, elderly normal group, were people who accompanied them. Some inpatients who did not have eye disease were also tested. All people accepted for testing wore their normally prescribed optical correction (if any) for near vision. All testing was monocular. The untested eye was patched. The normal persons had no signs or symptoms of eye disease and no family history of glaucoma. All patients had an ocular examination on the day of the test. We did not test those patients whose notes indicated they had severe glaucoma or bilateral field losses which included the macula. No eye drops, other than normal medication, were applied prior to testing. Other criteria for the selection of patients varied and are given before the 2 studies where clinical groups are involved.

Experiment 1

There were reports that the loss originally found with the Arden test[1 2] could not be detected with static oscilloscope displays[9] or when elderly glaucoma patients were compared to an age matched control group.[14] We therefore first compared the contrast sensitivity of glaucoma patients and age matched normal controls, using an oscilloscope to display static gratings at a wider range of spatial frequencies than were available with the printed tests.

METHOD

To minimise the degree of glaucoma and normal age change we only tested the better eye of each subject, for example, that eye with the least field loss or with the best visual acuity when field losses were equal or absent. Contrast sensitivities were measured by the procedure described above at a spatial frequency of 0·25 cycles/deg and in octave steps to 8 cycles/deg. Measures were also made with 2 cycle/deg square wave luminance profile stripes*. We measured 4 sets

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*Dr J. Robson had predicted that contrast sensitivity losses in glaucoma would not depend on the spatial frequency composition of the stimulus, for example, the difference obtained when testing with sinusoidal gratings should be no larger than that which occurred when square waves, which contain additional high spatial frequency components, were used. This was confirmed.

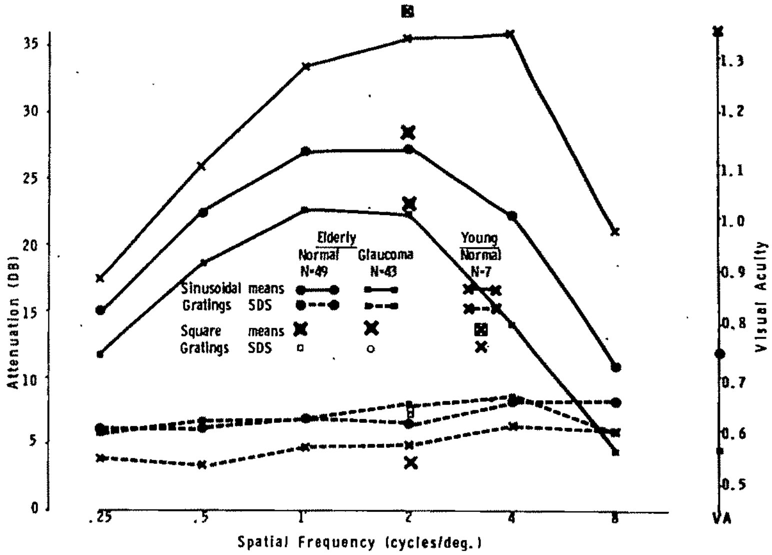

Fig. 1 *Means and standard deviations for all 3 groups at all 6 spatial frequencies tested with sinusoidal luminance profile gratings and with square wave luminance profile gratings at 2 cycles/deg. Note that the loss in glaucoma is roughly equal at all spatial frequencies and there is an associated deficit in near visual acuity. Although the loss is significant when the 2 groups are compared across spatial frequencies, separate comparisons at higher spatial frequencies become less significant because variance increases. The acuity difference is significant, as is the drop in contrast sensitivity with age.*

of threshold contrasts for the 7 stimuli and near visual acuity.

SUBJECTS

Seven normal young adults (mean age 24·6 years, SD 3·4, range 21–28, 4 males and 3 females, 3 right eye and 4 left, 2 needing normal near optical correction, mean visual acuity 1·36, SD 0·19, range 0·94–1·5) were tested on the apparatus to confirm that the test gave results similar to those normally reported. All the other people tested were over 50 years of age. Selection and testing were as outlined above. There were 49 normal elderly people (mean age 63·0 years, SD 8·5, range 50–82, 16 males and 33 females, 25 right eyes and 24 left, 45 needing normal near correction, mean visual acuity 0·75, SD 0·28, range 0·1–1·5) and 43 glaucomatous patients (mean age 68·8 years, SD 9·6, range 50–82, 21 males and 22 females, 25 right eyes and 18 left, 31 with normal near optical correction, mean visual acuity 0·57, SD 0·23, range 0·144–1·0).

The diagnoses were as follows: chronic simple glaucoma 29 cases (1 atypical), 2 ocular hypertensives, 8 subacute closed-angle glaucoma (in 4 cases an acute attack had occurred in the other eye), 2 thrombotic glaucoma, 1 secondary, and 1 of unknown aetiology. None had suffered an acute attack in the tested eye. The average time since diagnosis was 5·6 years (SD 5·6, range 0·3–29, 18<2). Cupped discs had been observed at some time in 29 (63%). Bjerrum screen fields with the 2/2000 target were full to 25 deg in 15 cases, slightly constricted in 8 (nearest point to the macula 18–25 deg), moderately constricted in 8 (12–18 deg), a large step in 9 (4–15 deg), and very constricted in 3 (2–5 deg). Those with more severe field losses were included because they had in general retained better visual acuity than some of the apparently less severe field losses. Mean maximum recorded intraocular pressure was 29 mmHg (SD 6·8, range 20–45) and on the testing day the mean was 18·6 mmHg (SD 5·4, range 10–38). Of the 19 cases in which pressure was surgically controlled, mostly by trabeculectomy and in some cases by peripheral irredectomy, only 5 received ocular medication (acetazolamide in 2 cases). In 17 of the other 24 cases some medication was used. No drug was used by 23; 13 took pilocarpine in various doses and therefore had miotic (very small) pupils when tested; 5 took timolol and 2, as noted, acetazolamide. Ocular complications among the patients were normal for this age group: 8 had early cataract, 1 was aphakic, 1 had a mild diabetic retinopathy, 1 had previously suffered from scleritis, and 1 had undergone cryosurgery to prevent retinal detachment such as had already occurred in the fellow eye.

RESULTS

Practice caused no change at all in the average threshold at any spatial frequency for any age group. Fig. 1 shows, for all groups, average contrast sensitivity and its standard deviation. Average near visual acuity is on the right margin. The maximum sensitivity (36 db or 1·6%) and extrapolated cut off spatial frequency (23 cycles/deg) of the young adults is similar to a comparable, normal, naive group.[24] (In laboratory experiments sensitivity can be above 40 db attenuation (under 1% contrast) and cut off spatial frequency above 30 cycles/deg (1 min arc). Scores were lower in our conditions because contrast was turned up on all trials (ascending method of adjustment), bracketing was not permitted, and the observers were unpractised.)

As spatial frequency increased, a large number of elderly people, particularly patients, said they could not see gratings well within the resolution limit expected from their visual acuities. This is why we did not test higher spatial frequencies. Furthermore, even with the 8 cycles/deg stimulus they inspected the target at 100% contrast for some time before saying they could see the grating. Slow responding is common to all elderly people, and when the contrast can no longer change it further biases the measure.

Analysis of variance of the elderly subjects' scores shows that the glaucomatous group have a significant 6 db sensitivity loss (a factor of 2) for all stimuli. There is a slight but significant tendency for differences to increase with spatial frequency and the patients also have a significantly lower visual acuity. The scores of the elderly normal persons and glaucomatous patients overlap substantially. If we set a rather lax false positive rate of about 6–10%, the 0·25 cycle/deg stimulus picks up 30% of the glaucomas. The correct assessment increases with spatial frequency to 44% with 8 cycles/deg, but this is a trivial consequence of the biased behaviour at higher spatial frequencies noted above. If the aggregate over spatial frequencies is used, the discrimination is marginally better (42% correct assessments to 6% false positives). These figures are of course only approximations and depend critically on the chosen cut-off in what is still a relatively small, mildly affected group in which only the better eye was tested.

When the young and elderly normal subjects were compared (Fig. 1), older people's sensitivity was 3–15 db lower and standard deviations were larger. The different behaviour at higher spatial frequencies noted above must contribute to this pattern. The standard deviation of scores increased by 50% with spatial frequency in all groups.

The average correlations between all variables are shown in Table 1. Because each setting was repeated 4 times there were 6 separate pairs from which reliabilities were calculated (on diagonal cells) and 16 pairings of any 2 spatial frequency settings to estimate their correlation (off diagonal cells). The reliability of the measure at any spatial frequency is about 0·75. The increased reliabilities at higher spatial frequencies is simply due to some subjects slowly responding to maximum contrast, as noted above. Not surprisingly, the correlation between sensitivity scores increase as the spatial frequencies at which the measures were made become more similar. In contrast, the correlation between visual acuity and contrast sensitivity is low and equal for all spatial frequencies. It is more highly correlated with age, an observation which will recur later. The correlation of sensitivity with age is −0·1 at 0·25 cycle/deg and −0·51 at 8 cycles/deg. This shows that contrast sensitivity decreases as age increases and the effect is more marked at higher spatial frequencies.

DISCUSSION

Our results are in accord with most studies using printed tests but disagree with the findings of Atkin *et al.*[9] and Sokol *et al.*[14] Glaucoma patients do have a contrast sensitivity deficit of about 6 db in relation to age matched normal persons at all spatial frequencies when tested with a conventional oscilloscope display of static gratings. We also found that visual acuity and contrast sensitivity for square wave gratings were similarly reduced in glaucoma by about 6 db. There is evidence that luminance gradients determine low spatial frequency detection.[25] The central retina would be able to do this best. Our data similarly are against the view that peripheral retinal damage is especially revealed by tests at low spatial frequencies[2]

Table 1 *Average correlation between repeated oscilloscope settings to standing sinusoidal gratings at 6 spatial frequencies, plus age and visual acuity. On the diagonal are means of 6 reliability estimates (4×3/2) and off it means of 16 correlations (4×4). Reliabilities at high spatial frequencies are artificially high for reasons given in the text. Correlation drops systematically as stimulus differences increase. Visual acuity fails to follow this general trend and correlates better with age.*

			Spatial frequency (cycles per degree)							
			0·25	*0·5*	*1·0*	*2·0*	*4·0*	*8·0*	*VA*	*Age*
		0·25	0·68	0·65	0·56	0·48	0·39	0·36	0·27	−0·10
S	F	0·5		0·76	0·71	0·63	0·54	0·48	0·31	−0·19
P	R	1·0			0·78	0·68	0·58	0·55	0·35	−0·32
A	E	2·0				0·80	0·71	0·62	0·34	−0·37
T	Q	4·0					0·88	0·79	0·34	−0·45
		8·0						0·86	0·38	−0·51
		VA							—	−0·56

SPAT/FREQ in left-hand column=spatial frequency (cycles per degree).

but do show why these stimuli are clinically useful.

The significant loss of visual acuity we found associated with glaucoma was so small as to be of no clinical importance in any individual case. Visual acuity and cut off spatial frequency are 2 measures of the resolution limit. Our observation that they are often poorly correlated and may measure largely separate abilities has been made previously.[26] In disease either may be more severely reduced.[26 27] When the cause of this discrepancy is known, comparing both measures may be clinically useful. Sensitivities for quite moderate spatial frequencies (above 2 cycles/deg)[11] as well as the resolution limit[15 28] can be seriously affected by many optical and neural variables which are hard to isolate and control. Gratings of still lower spatial frequencies are clinically useful because they are less sensitive to these factors.

Low spatial frequencies offer advantages for other reasons too. We used what are ordinarily considered quite moderate spatial frequencies. Nevertheless we found that as spatial frequency increased so did variability. These increases were associated with behavioural changes and were greater for older people. For this reason alone disease may cause larger deficits at higher spatial frequencies, but larger samples will be necessary to detect them. This might explain why visual acuity is sometimes said to be unchanged in glaucoma and why some studies have not found significant differences. The significance of loss of contrast sensitivity at any spatial frequency will therefore depend on sample size and the degree to which these biases are present in the test used. Nevertheless we found that these high frequency biases were not very evident when square wave luminance profile bars were used. If this were to be confirmed, future clinical contrast sensitivity tests could be considerably simplified.

Contrast sensitivity, measured by the Arden test, decreases with age.[12–14 16] These oscilloscope settings also decrease with age, as do those of Beasley *et al.*[24] We believe that age trends may be greater with subjective methods, for reasons given below.

Experiment 2

Having confirmed that glaucoma patients do show contrast sensitivity loss, we wanted to establish what method of testing contrast sensitivity would provide the most clinically useful index of reduced function. There are obvious advantages to printed tests, and we wanted to see if the 4AFC format described above justified further development. There are 5 criteria, defined above, by which tests can be formally and experimentally evaluated.[29 30] Three separate studies were necessary before comparisons could be made using all 5 criteria. In this experiment the test results of a large group of normal people were analysed to see how the several tests compared. In experiment 3 we repeatedly tested normal people with the 2 printed tests to see if the scores of an individual changed. Finally in experiment 4 we looked at the effect of age and glaucoma on the printed tests results to see which was most useful in practice.

METHOD

Thirty-six normal people of a wide range of ages (mean 35·2 years, SD 21·2, range 5–82) were tested on the 2 printed tests and the oscilloscope display with static and 4 Hz phase reversing gratings set to the same 6 spatial frequencies using the same 28·5 cm testing distance. Test procedure and subject selection were as described above. In each test, gratings of the various spatial frequencies were presented in random order. Each of the 4 tests was completed before another, selected at random, began. Both eyes were tested successively, and the order was reversed for each test. With the oscilloscope test 5 threshold values were obtained and averaged. Visual acuity at 'near' (Sheridan-Gardiner Singles) (mean 0·75, SD 0·22, range 1·0–0·25) and 'far' (Snellen) (mean 0·92, SD 0·34, range 2·0–0·25) was also recorded. For statistical purposes all 72 eyes were treated separately. There were scores on 27 variables for each eye (4 methods×6 spatial frequencies, plus 2 visual acuities and age).

We made the measurements in this way because such data are best suited to a later analysis which can tell us about the relationship between the tests. The average score of the group on each variable is of little interest, because any measure is made only once and any treatment which might change it is avoided. Instead the first step is to calculate all possible correlations between variables. In this experiment there were 351 of them (27×26/2). Such a large set of numbers is incomprehensible unless general patterns can be found. Some obvious patterns can be shown by averaging subsets of the correlation matrix.

Factor analysis[30] is a more precise way of describing these interrelations. It is a mathematical method for formally analysing the correlation matrix, which reduces a large number of variables to a smaller set of hypothetical sources of variation (called factors). Highly correlated variables share more factors in common. Each variable is given a loading on each factor which shows how the variable would correlate with the factor if it could be directly measured. The experimenter can then characterise the factor from what he knows about the variables. If the raw scores are multiplied by the factor loadings each subject can be given a score on each factor so that a large number of test scores can be reduced to a much smaller

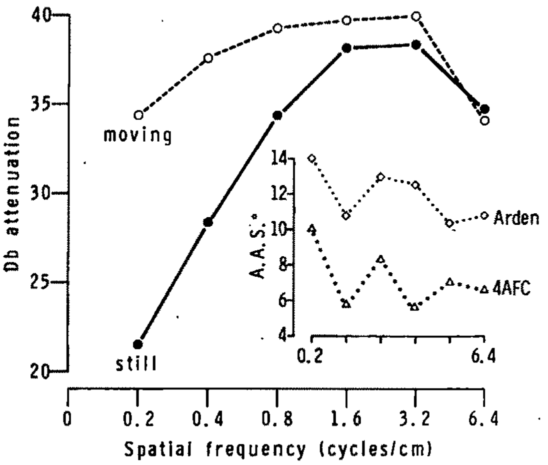

Fig. 2 *Average scores on the 4 contrast sensitivity tests for all 74 eyes in experiment 2. Scores on the printed tests do not converge at high spatial frequencies as the 2 oscilloscope test scores do, which suggests that the systematic difference between them is not associated with movement cues caused by different inspection strategies. Contrary to the db attenuation scale, higher scores on the arbitrary scale provided with the printed tests imply poorer performance.*

number of factor scores, considerably simplifying later analysis.

RESULTS

The investigation was not directly concerned with the average scores. They are presented in Fig. 2 merely to show that the values are normal. The static grating results are similar to the young adults' scores in the previous experiment and other studies as discussed above. The different curves found with static and phase reversing gratings, especially at low spatial frequencies, may also be expected from previous work.[31] The 2 printed test curves are shown as an inset. Note that here higher scores imply less sensitivity. The means and standard deviations we obtained on the Arden test are very similar to those in previous studies[1 2] despite the minor procedural changes.

Table 2 shows the average over all tests of correlations between spatial frequencies. The same pattern was found for each test. As in the previous experiment (Table 1) all correlations are high, and closer spatial frequencies were more highly correlated.

Table 3 gives the average correlation between tests irrespective of spatial frequency. The mean correlation between scores at 2 different spatial frequencies in the same test (on diagonal cells) is much greater than that between all scores from different tests (off diagonal cells). (Because correlations are high within a test the numbers in the cells on the diagonal of Table 3 are a function of each method's reliability but must be smaller than the correct figure. Thus the previous estimate of reliability for a single oscilloscope setting (0·68–0·88, Table 1) is greater than the average over all spatial frequencies here (0·61). A comparison is possible

Table 2 *Average across all tests of the correlation between 2 spatial frequencies in the same test. Each number is the mean of 6 correlations (4×3/2). Signs have been inverted for all results involving the Arden or 4AFC test so as to eliminate the negative correlations which would otherwise result, because higher scores on these tests imply worse sensitivity. The correlation generally decreases slowly with increasing difference in spatial frequency.*

		Spatial frequency (cycles per degree)					
		0·1	*0·2*	*0·4*	*0·8*	*1·6*	*3·2*
	0·1	—	0·59	0·56	0·51	0·40	0·34
S F	0·2		—	0·57	0·58	0·51	0·46
P R	0·4			—	0·62	0·52	0·44
A E	0·8				—	0·62	0·51
T Q	1·6					—	0·64
	3·2						—

Table 3 *Average correlation between all test pairs across all spatial frequency pairs. On the diagonal is the average of the 15 correlations between spatial frequencies within a test (5×6/2). Because the correlation decreases slowly with increasing difference in spatial frequency (Tables 1 and 2), these figures are lower bound estimates of reliability, even though the correlation of a spatial frequency with itself is excluded. Thus the visual acuity 'reliability' is only the correlation of measures at near and far. Each number off the diagonal is based on 36 between test correlations. The correlations remained relatively constant where each plate came from a different test and are generally lower than those between widely separated spatial frequencies from the same test. Standard deviations were about 0·1, and there was less systematic variation with difference in spatial frequency than for within-test correlations.*

		Test					
		4AFC	*Arden*	*CRO at 4 Hz**	*CRO static†*	*Visual acuity*	*Age*
	4AFC	0·40	0·24	−0·36	−0·24	−0·16	0·17
T	Arden		0·40	−0·31	−0·20	−0·10	0·18
E	CRO at 4 Hz			0·68	0·45	0·28	−0·18
S	CRO static				0·61	0·19	0·21
T	Visual acuity					0·48	−0·28

*Gratings generated on a CRO (cathode ray oscilloscope), phase reversing at 4 Hz.
†Gratings generated on a CRO which remain stationary.

Table 4 *Orthogonal, varimax rotated factor structure obtained for 74 eyes tested on 27 variables in experiment 2. All loadings of 0·3 or more have been printed in bold so that the pattern of loading on each factor can be seen at a glance. Similar solutions for the relationship between the 2 printed tests, visual acuities, and age was found in all subsequent sets of data.*

Factor Variable (cy/deg)		*CRO static*	*CRO at 4 Hz*	*4AFC*	*Arden*	*Arden High SF*	*Near blur*	*Visual acuity*
	0·1	0·21	−0·02	**0·67**	0·30	0·11	0·12	−0·28
4	0·2	0·13	−0·04	**0·64**	0·13	−0·20	0·08	−0·10
A	0·4	0·12	−0·27	**0·74**	0·19	0·07	−0·13	−0·02
F	0·8	−0·01	**−0·32**	**0·73**	0·12	−0·12	−0·22	0·10
C	1·6	−0·02	**−0·37**	**0·64**	−0·19	−0·27	−0·13	0·12
	3·2	0·29	−0·21	**0·33**	0·00	−0·23	**−0·65**	−0·04
A	0·1	−0·11	−0·17	0·26	**0·77**	−0·02	−0·06	0·04
R	0·2	0·17	−0·09	0·28	**0·66**	**−0·34**	0·07	0·11
D	0·4	0·04	−0·02	−0·07	**0·83**	0·00	−0·06	−0·17
E	0·8	0·11	−0·13	0·20	**0·62**	−0·24	−0·18	−0·24
N	1·6	**0·30**	−0·16	0·06	**0·33**	**−0·74**	−0·08	−0·02
	3·2	0·06	**−0·30**	0·20	0·12	**−0·72**	**−0·30**	−0·12
	0·1	−0·15	**0·79**	−0·26	−0·22	0·10	−0·08	−0·04
C 4	0·2	**−0·34**	**0·79**	−0·19	−0·08	0·02	0·02	0·17
R	0·4	−0·25	**0·80**	−0·17	−0·05	0·08	0·06	0·13
O H	0·8	**−0·31**	**0·72**	**−0·30**	−0·12	0·27	0·17	0·03
at z	1·6	**−0·40**	**0·64**	−0·15	−0·14	**0·34**	0·22	0·22
	3·2	**−0·34**	**0·59**	−0·05	−0·14	0·15	**0·48**	0·20
S	0·1	**−0·71**	**0·34**	−0·04	−0·03	−0·28	0·18	−0·01
C T	0·2	**−0·79**	**0·35**	−0·06	−0·20	−0·01	−0·07	0·00
R A	0·4	**−0·81**	**0·33**	0·00	−0·11	0·03	0·05	−0·05
O T	0·8	**−0·78**	0·13	−0·12	0·02	0·25	0·20	−0·10
I	1·6	**−0·78**	0·05	−0·16	0·07	**0·37**	0·13	0·19
C	3·2	**−0·68**	0·19	−0·20	0·04	0·27	**0·30**	0·23
Visual	Far	0·00	0·24	−0·14	0·09	0·07	0·07	**0·84**
Acuity	Near	−0·15	0·09	0·12	−0·09	0·10	**0·67**	**0·57**
Age		0·11	0·02	0·03	0·10	−0·06	**−0·88**	0·03
% Variance used		16	16	11	10	8	9	6

because all estimates are similarly reduced, but both oscilloscope scores may appear more reliable than either of the printed test scores only because they are an average of 5 settings.) The correlation was always small and did not clearly increase for closer spatial frequencies when they were presented in different formats. Nevertheless all these measures of contrast sensitivity are yet more poorly correlated with visual acuity. It correlates best with age. The same pattern was found in experiment 1 (Table 1). Thus low spatial frequency contrast sensitivity can be regarded as a distinct ability, although there are other nonrandom variables, peculiar to each test, which affect the score.

Similar conclusions can be more directly derived from a factor analysis of the data from the current experiment (Table 4). Factor loadings of 0·3 or greater are printed in bold. We can then clearly see a pattern in which a major factor is associated with each testing method, the oscilloscope tests are very similar, and the 2 printed tests have more in common with either oscilloscope test than with each other. There are 3 minor factors all concerned with visual acuity. One is clearly 'pure' visual acuity, since it loads on the highest spatial frequencies and both visual acuity tests. The next is involved with 'near' vision, high spatial frequencies, and changes with age (apparently presbyopia but called 'near blur' because it is also found in children's data in other studies). The last is peculiar to the Arden test.

To identify features which might affect the result we made a list of all the recognisable differences between the 4 tests (Table 5). No single feature easily explains the obtained pattern of correlations, but if the total number of countable differences is low, the correlation tends to be higher. Therefore any set of methodological difference may be important.

DISCUSSION

An individuals's performance on contrast sensitivity tests with gratings of 1·6 cycles/deg or lower is so loosely related to both visual acuity and optical

Table 5 *Systematic differences between the 4 contrast sensitivity tests used in experiment 2 which might influence the way subjects respond.*

1. Stationary (4AFC,A,S) vs. moving stimuli (M)
2. Accuracy checked (4AFC) vs. subjective psychophysics (S,M,A)
3. Descending (4AFC) vs. ascending (A,S,M) contrast series
4. Some oblique (4AFC) vs. all vertical (A,S,M) grating orientation
5. High spatial frequencies in small (4AFC) vs. large (A,S,M) areas
6. Low spatial frequencies have few (4AFC) or many (A,S,M) cycles
7. Smooth pursuit (A) vs. free search (4AFC,S,M) eye movements
8. Viewing time limited (A,S,M) vs. free (4AFC)
9. Patterns printed, dull and reflected (4AFC,A) vs. electronic, bright and emitted (S,M)
10. Well lit room (4AFC,A) vs. dark room (S,M)
11. Examiner directed (4AFC,A) vs. self-controlled (S,M)

S=static gratings on the oscilloscope. M=moving gratings on the oscilloscope. A=Arden's test.

factors[15] that it must indicate a distinct ability. However, there are such substantial differences between the subject rankings obtained in the various tests that we cannot decide which of them is the best measure.

The 2 tests employing the oscilloscope display give results which are closely related statistically, even though the appearances of static and contrast reversing gratings are very different; the difference between the means varies systematically with spatial frequency, and it is often thought that they can differentially stimulate separate visual channels.[32] On the other hand the 2 tests where the stimuli are cut from the same printed sheets give poorly related scores when only the layout and testing method differed.

Experiment 3

A clinical test should be as accurate as possible. In terms of the formal criteria defined above there are 2 sorts of accuracy to consider: reliability and stability. We had estimated these qualities for the static oscilloscope test but only made a coarse, lower-bound estimate for the others. We knew that the static and phase reversing gratings gave highly correlated results. We suspected that the coarse reliability estimates for the printed tests appeared less reliable than those for the oscilloscope settings only because the latter were based on the mean of 5 scores. We therefore concentrated on the reliability and stability of the 2 printed tests. They represent extreme differences in procedure and factor structure while sharing great practical advantages.

METHOD

We assessed both eyes of 28 normal young adults (mean age 31·1, SD 6·53, 12 M, 16 F) on both tests 3 times. The starting eye and test were chosen at random. All testing was completed on the first eye before the other was used. The order of spatial frequencies within each test was randomised, but all 6 were completed as a block before the next test began. The 2 tests were then presented alternately for 3 cycles. Testing procedures were as previously described.

RESULTS

By treating eyes and spatial frequencies separately we can concentrate on the relations between the 3 repetitions of the 2 tests. From the 6 scores 15 correlations can be calculated. Three are correlations between 4AFC scores on different occasions (the test-retest reliability for each 4AFC plate). Three similarly are for the Arden test. The remaining 9 estimate the between-test correlation. The average of each of these sets at each spatial frequency is shown in Table 6. Clearly the 4AFC test is more reliable than the Arden test, except at the 2 extreme spatial frequencies. Moreover, in the same range its reliability is as good as or better than that determined for oscilloscope settings in the first study (Table 1). The 4AFC test appears less reliable in those conditions where the discs are small or the number of cycles presented very low. Thus it can be attributed to inadequate stimulation and the image degradation from print imperfections and mounting technique. While the problem could be removed in principle, we have seen that these spatial frequencies are the least useful ones.

In the previous experiment a single printed test measure appeared less consistent than the average of 5 oscilloscope settings. In this study, when the 3 replications were averaged first and the same parameter calculated, the value was 0·747 for the 4AFC test and 0·612 for the Arden test. This 4AFC estimate, based on 3 replications, is better than the highest oscilloscope estimate, based on 5 (0·684 for the moving gratings). Clearly not only is averaging

Table 6 *Average of 3 test-retest reliabilities from 3 replications of each plate in the 4AFC and Arden tests and average between-test correlations (based on all 9 pairs). The original correlations are based on the scores from 56 normal young adults' eyes, tested 3 times with each of the printed tests.*

Spatial frequency (cycles per degree)	0·1	0·2	0·4	0·8	1·6	3·2
Average 4AFC reliability (n=3)	0·69	0·75	0·74	0·82	0·69	0·65
Average Arden reliability (n=3)	0·76	0·51	0·48	0·59	0·66	0·74
Average intercorrelation (n=9)	0·27	0·36	0·22	0·12	0·09	0·34

several replications the key to increased reliability, but by both estimation procedures the 4AFC test's reliability equals or exceeds that of the other 3.

While reliability is the tendency for a subject to retain the same score relative to the others in the group when the test is repeated, stability implies that the mean and standard deviation of the group does not change when the test is repeated. In the Arden test there is a significant tendency for subjects to appear more sensitive on successive trials, but it is small (0·75 units of the arbitrary scale, or 1·2 db) and becomes significant only when the results of all spatial frequencies are combined. For this reason it was previously reported to be insignificant.[16] The trend is insignificant for the 4AFC test under either analysis.

Analysis of other aspects of the data, not explicitly related to the results of successive testing, served simply to confirm the results of the previous experiment. Mean scores and variances were similar. Correlations between tests were of the same magnitude and had the same factor structure whether raw scores or averages were considered. Because the different factor structures are consistent, the tests must measure somewhat different faculties.

Experiment 4

Having established that printed tests gave reliable, stable measures and that the 4AFC format and procedure indeed appeared to be an improvement, we wanted to see if it was also better in practice. Clinically useful tests should have generalisable normal values, as defined above, that is, the normal average score and range of variability should not change with age (or socioeconomic group or motivation level). Moreover it should be efficient, that is, people judged clinically to be mildly affected or at risk should frequently fall outside these limits.

We assessed both eyes of many normal subjects (using both tests once only), until we had sufficiently large numbers in 3 age ranges. We included in this series subjects used in the 2 previous experiments. Only the first set of measures from experiment 3 was used. There were 21 children (9 M, 12 F) between 3 and 15 years of age (mean age 8·73, SD 3·64), 55 adults (25 M, 30 F) between 22 and 49 (mean age 32·9, SD 8·7) and 21 elderly people (11 M, 10 F) between 50 and 82 (mean age 60·9, SD 8·75). We also assessed both eyes of 24 glaucomatous patients (13 M, 11 F) between 52 and 83 years of age (mean age 65·25, SD

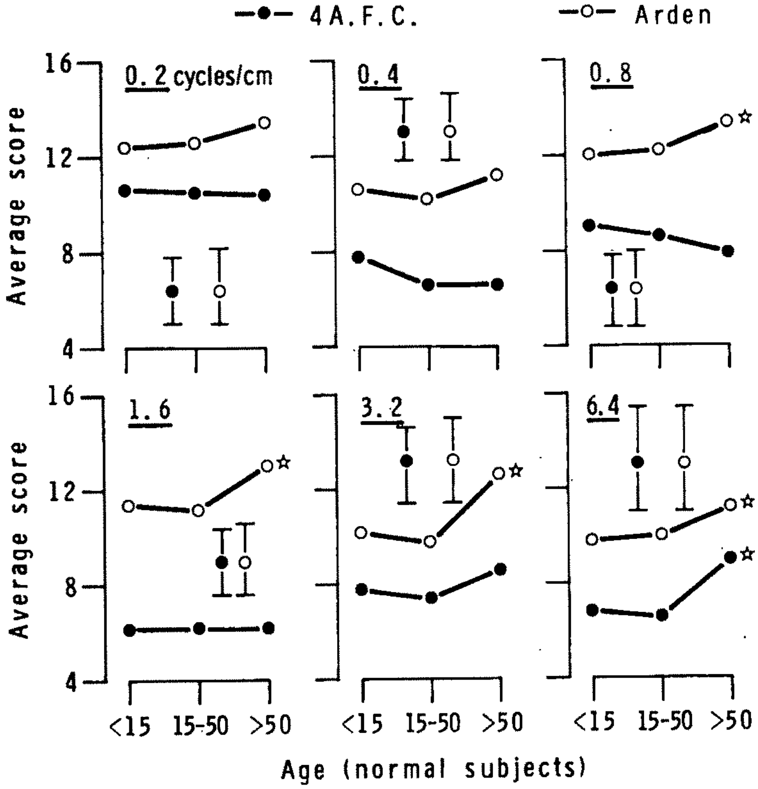

Fig. 3 *Age changes in the Arden test (open circles) and the 4AFC test (black circles) at each spatial frequency. Stars indicate significant age trends. Vertical bars represent one standard deviation. Note that there is a consistent and mostly significant trend for elderly people to perform more poorly on the Arden test, while this occurs only at the highest spatial frequency for the 4AFC test. Also note that standard deviations increase with spatial frequency.*

10·35). In all cases at least one eye was clinically judged to be only mildly affected.

The group of patients included 8 symptom-free ocular hypertensives and 3 cases of chronic simple glaucoma, with no loss of visual function or clinical signs except raised pressures and slight cupping in either eye. Of these 11, 4 were receiving medication, which was a miotic in 3 instances. The other patients were diagnosed as chronic simple glaucoma (7), closed-angle glaucoma (5), and Posner-Schlossman syndrome (1). The pressure was controlled surgically (3 cases), by miotic drugs (3), nonmiotic drugs (3), both surgery and miotic drugs (1), and surgery and nonmiotic drugs (2). In 3 cases only 1 eye was being treated. Visual symptoms of these 13 ranged from no (4) to at worst moderate visual loss in the better eye and moderate to severe loss in the worst eye. Moderate here means a field loss intruding no closer than 10 degrees to the macula, associated with cupping of the discs, raised intraocular pressures, and a drop in far visual acuity to no less than 0·5. Seven eyes were severe, that is, with field loss including the macula. These 7 eyes failed to detect any plate on either test, and the scores therefore simply reduced the significance of any differences which were observed.

RESULTS

We first looked for any age trend in the scores of all normal subjects (Fig. 3). Sensitivity only decreased with age at the highest spatial frequency in the 4AFC test. However, there was a clear decrease of the Arden test scores with age at all spatial frequencies. Analysis of variance showed this effect to be insignificant for plates 2 and 3. Variance again increased with spatial frequency.

We then compared the mean scores of the glaucoma patients with the age matched, normal, elderly control group for each plate separately (Fig. 4, top) and established the significance of these differences by analysis of variance. The glaucoma patients had significantly reduced sensitivity to each

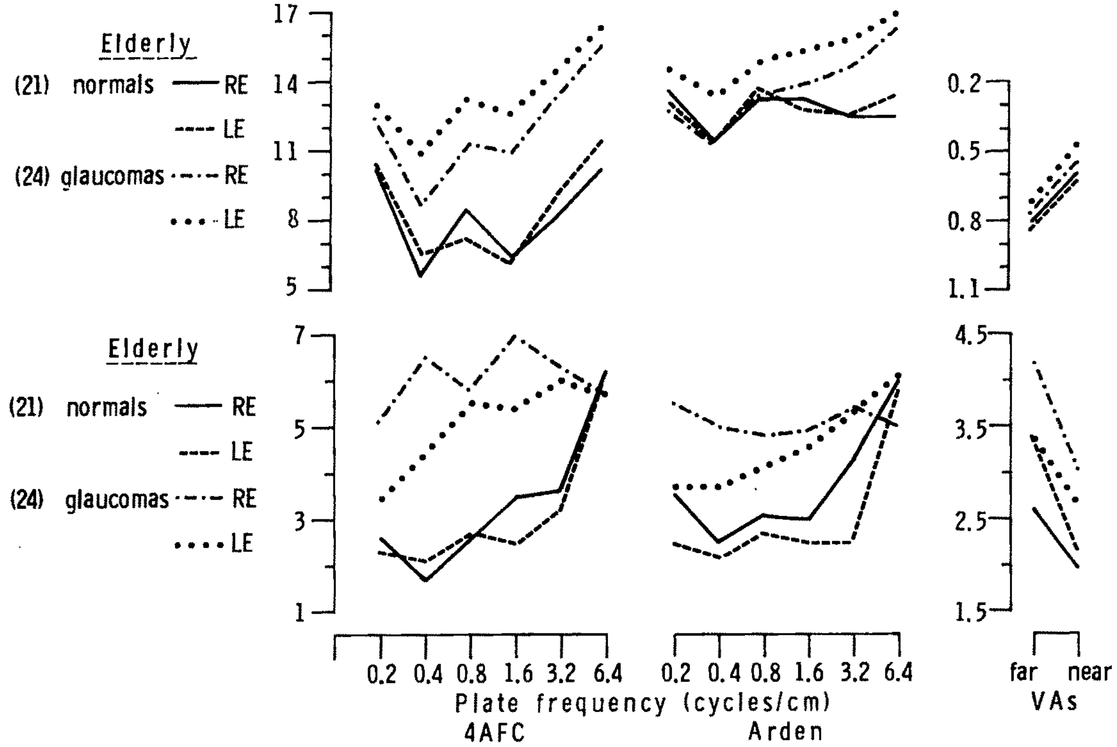

Fig. 4 *Means (top row) and standard deviations (bottom row) for right and left eyes of the normal and glaucomatous elderly patients tested on the 4AFC test (left column) and the Arden test (middle column). Near and far visual acuities are given at the far right. Note that the difference between patients and normal persons can be seen even in the visual acuity scores and is slightly greater at high spatial frequencies in both printed tests, but the effect is very small. In the 4AFC test there is a general loss averaging about 4 Arden units (6·4 db) across all spatial frequencies. The standard deviations are high partly because 7 eyes with macular involvement have been included, and this has reduced the difference between the 2 tests.*

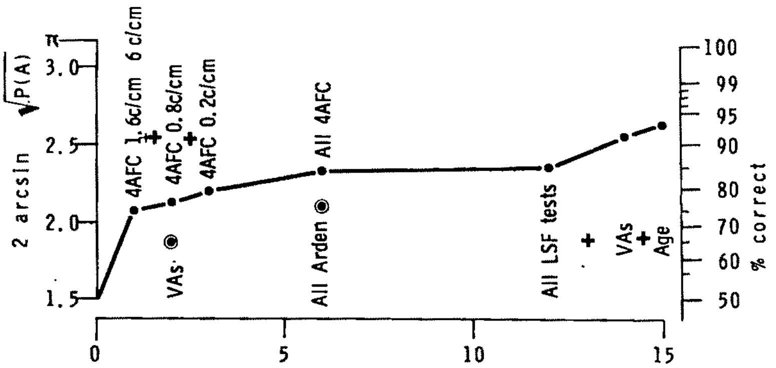

Fig. 5 *A nonparametric measure of signal detection sensitivity (2 arcsine (square root P (A))) plotted as a measure of information efficiency for various subsets of the measures taken on elderly normal or glaucomatous patients. The measure relates separations of all subjects based on the data subset to the original clinical categories. If a large number of assumptions are made, this score is monotonically but nonlinearly related to the better known criterion of percentage correct, the scale for which is given on the right. Note that visual acuity detects patients more poorly than either contrast sensitivity test, and that one plate of the 4AFC test is more effective than the complete Arden test.*

separate 4AFC plate averaging about 4 Arden units (6·4 db), which is not unlike the difference found in experiment 1, with very different equipment and psychophysics. When the Arden test was used, the glaucoma patients appeared to have reduced contrast sensitivity for only the highest spatial frequency plate. There was a significant effect in the Arden test if it was scored as prescribed.[1,2] The mean aggregate score for normal elderly people (50·3) was significantly below the mean aggregate score for the glaucoma patients (76·2) ($p<0·001$, DF 88) despite the use of 21 rather than 25 as the default score when plates were not seen.

This analysis of the effects of glaucoma on average score is complicated by the standard deviation for the glaucoma patients' scores being much higher than the normal controls', except at the highest spatial frequency, where it is high for both groups (Fig. 4, bottom). Glaucoma did not increase the standard deviation in experiment 1. Some of this effect must be due to the inclusion of the 8 eyes with macular involvement in this part of the analysis. They could not detect any grating in either test and were given scores of 21. The differences between the 2 tests would have been more extreme if these data had not be included.

As in experiment 1 and previous reports[1,14] we found with both tests that the mean difference between groups was slightly greater at higher spatial frequencies. The differences between the visual acuities of the normal and glaucomatous subjects, while of the same magnitude as that found in experiment 1, was not significant here because the sample size was smaller. The finest stimulus used in the contrast sensitivity tests, it should be recalled, was 3·2 cycles/deg, well below the acuity limit. This demonstrates how a real difference may exist at all spatial frequencies but still appear to be restricted to low ones where variances are less.

Although the mean difference between glaucomatous patients and age matched controls is greater with the 4AFC test, we wanted to show directly how much more diagnostic information it contained*. We first estimated precisely how much more efficient this information is in the formal sense defined above. In Fig. 5 we have plotted both efficiency and predicted percentage correct against increasing numbers of plates for both tests. It is clear that either printed test detects glaucoma more efficiently than a visual acuity test can. Moreover one plate of the 4AFC test on its own is more efficient than the complete Arden test.

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*In this formal analysis we first used stepwise multiple regression to see which variables were most heavily correlated with having glaucoma. Discriminatory analysis was then used. It acts on the set of supplied data (here the selected set of scores) and classifies all the elderly subjects into 2 groups, the size of which was specified to be the same as the original clinical classes. It chooses 2 groups which are as different as possible on the basis of the data available to it.[30] We then took the variables in various sets, starting with the most effective in each of the 2 tests, or with visual acuity, and adding more variables in the order given by the stepwise multiple regression.

The discriminatory analysis of any data subset provided us with a mathematically derived classification which could be compared with the original clinical categories in a 2×2 table. The 4 cells of this table correspond to correct assessments, false alarms, misses, and correct rejections of a signal detection task.[33] Such tables can be converted into a nonparametric measure of sensitivity. Sensitivity in this sense is a precise measure of the efficiency with which the available information can be used to make a decision. If a large number of assumptions are made, it can also be used to predict the percentage of correct decisions which will be made.

Clinical decisions cannot rely on the calculation of complex formulae. While it must be stressed that this clinical study was a very preliminary trial to see if either test format produced larger differences in mean scores between patients and normal persons, the data can be looked at in more detail. As in experiment 1 we can use the raw scores in association with an arbitrary cut-off to establish approximate correct detection and false positive rates. The Arden test is scored in an entirely comparable manner.

Detection rates were calculated for all 41 eyes without macular involvement and for the 24 affected persons, the eye with the maximum score being used except for the 7 cases with macular involvement. False positive rates were calculated for the 42 elderly normal eyes and (because there is no substantial age trend) for the total normal sample (194 eyes). The figures for the least affected eyes are comparable to those found in study 1 provided we remember that there are different groups involved.

With a cut-off between 11 and 13 most 4AFC plates alone detected 30–45% of affected eyes and 45–58% of affected persons with false positive rates of around 5–7% for elderly normal persons and 2·5–4% for the total population. If we sum the scores of the middle 4 plates of the 4AFC test, which are the most reliable ones, only 1 of the 42 normal elderly eyes we tested scored 42 or more (2%). In the total sample of 198 normal eyes only 11 (5·6%) had scores above 44. If we take an aggregate of 44 as a cut-off, 39% of the affected eyes and 54% of the glaucoma patients are detected. Other studies will be required before we can decide whether this level of detection is sufficiently high or can be improved upon, but it is close to the mathematical optimum possible with the sophisticated procedure used to derive Fig. 5. The correct assessment rate is as good as or better than that obtained in experiment 1 with a test which takes almost 5 times as long on more expensive equipment, and the false positive rate is substantially lower. It remains lower even when a much wider age range is included in the normal sample.

We have examined the association between contrast sensitivity scored in this way and the clinical characteristics of 43 of the 48 eyes which were examined. Of the eyes with clear visual losses (apart from the 7 with macular involvement) 10/15 were abnormal. Even when there was no other visual loss 4/21 were abnormal. These 4 included 2 cases with severe loss in the other eye (1 closed angle, 1 chronic simple case); one other showed mild cupping, and the last had a highest recorded pressure of 38 mmHg. Contrast sensitivity loss can therefore be detected even in the very early stages of glaucoma. In general there was an association with both maximum recorded pressure and presence of any field defect, but perhaps because of the small numbers neither was significant (p=0·15). There was no clear association with either the use of miotic medication or a history of surgery, but again the sample is too small to be certain. Certainly significant losses could occur in eyes without either treatment. One eye in which there was substantial field loss but macular sparing failed to detect any 4AFC plate, while all the Arden test scores were apparently within normal limits. Such a case clearly underlines the advantages of forced choice testing methods.

DISCUSSION

Age related changes in contrast sensitivity are restricted to the 3·2 cycles/deg plate with the 4AFC procedure. Several previous authors have found that sensitivity decreased with age in the Arden test,[12–14 16] particularly with the higher frequency plates. We have confirmed that effect and shown that it generalises to ordinary oscilloscope settings. The sole difference between these studies is that the age trend extends to much lower spatial frequencies if subjective methods are used.

Contrary to these observations Sekuler *et al.*[17 18] reported that elderly people lose sensitivity to low but not high spatial frequencies. These authors appear to have carefully validated their data,[19] but several features of the experiment may have produced a wrong conclusion. Of these the most important is that their elderly group may not be a representative sample. The small number of subjects were carefully selected to have normal visual acuity and may therefore have come from a group with extremely high acuity prior to any age deterioration, without any necessary associated superiority at lower spatial frequencies. Other possible problems with these studies include small sample size, a very rapid rate of contrast change during measurement, the use of descending trials, and a failure to check that the estimated threshold was asymptotic.

W. Barnard, D. Powell, and R. Carter (personal communication), working in our Moorfields Clinic, have established norms for a computer-driven contrast sensitivity test on a large sample covering a wide range of ages. They found that the correlation between age and contrast threshold appeared increasingly above 1·6 cycles/deg, which supports the 4AFC test result. Their test was very similar to that used by Sekuler *et al.*[17 18] except that it did not have the biases we find in that study. Contrast was linearly ramped. Beasley *et al.*,[24] also using a similar testing method on a large sample, found that high spatial frequency deficits increase continuously at ages above 20. Visual acuity changes with age are well known and regularly found (reviewed by Devaney and Johnson[28]). There is a clear neurophysiological basis for this commonly observed visual acuity loss.[28] However, specific losses in the low spatial frequency range, while visual acuity remains within normal limits, have never been established in any clinical group with forced choice methodology and large samples. It seems unlikely that age alone would produce such a pattern.

Conclusions

There appears to be no special loss of low spatial frequency contrast sensitivity in glaucoma. The overall 6 db loss (a factor of 2) found in experiments 1 and 4 with very different tests also adequately accounts for the small differences in visual acuity which did occur. The visual acuity differences are not clinically significant in the individual at risk and reach statistical significance only in large samples. As shown above, the variability of contrast threshold determinations decreases at lower spatial frequencies. In this range factors like poor refraction and normal pupillary and lenticular changes also have less effect on the result. This is the main reason why low spatial frequency contrast sensitivity testing is useful. It is unwise to include stimuli of spatial frequency above 2 cycles/deg in such a test. There is no reason to believe that peripheral retina is more likely to be used.

It is possible that the sample was too small or unrepresentative in many studies which do not find significant differences.[4 9 14 17 18] Atkin *et al.*[9 10] may similarly have had greater success with phase-alternating stimuli because responses to them are more reliable (experiment 2).

Our experiments estimate 5 formal criteria which can be defined and measured so that the clinical value of tests can be compared: reliability, stability, generality, efficiency, and utility. The psychophysical method influences responses and ranking in a group more than differences in the stimulus, so that stable responses need not accurately reflect contrast sensitivity, and tests with checks on accuracy must prove clinically superior to those where a subject's report is taken at face value.

The 4AFC test we developed is only a prototype, but it is at least equal to all other testing methods on all the criteria by which a comparison has been made, and it is better than each other method on at least one criterion and the known weaknesses can be easily rectified. At most spatial frequencies a 4AFC measure is less variable and more reliable than one from an adjustment method. It gives scores which, relative to the Arden test, are more consistent across retests, norms which generalise to all age groups, and results which are more efficient in the practical aspects of glaucoma detection. Because it is similar to a sight test chart it has a familiar form, and high scores can be trusted. It is portable, inexpensive, fast, and simple to administer and score. This 4AFC test will help us design another, better, clinical test.

During this study Vaegan received support from the Garrick Foundation Trust for Research into Child Blindness, the East Anglia Regional Health Authority, and the Golden Nugget Fellowship at the Institute for Ophthalmology, London. He currently holds an MRC fellowship. Equipment support was provided by MRC grant C59 to C. Blakemore and P. G. Watson.

Professor G. B. Arden contributed by discussion and encouragement to every stage of this study and deserves special thanks. The authors also wish to thank Mr P. G. Watson and Mr J. Cairns for permitting them to examine patients in the clinic at New Addenbrooke's Hospital, Cambridge, and all staff members of that clinic who assisted with the ophthalmic examinations. Caroline Hawthorn-Thwaite and Jennifer French assisted with testing in experiments 2 and 3 respectively. Mr R. Hitchings kindly commented on an earlier version of the manuscript.

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British Journal of Ophthalmology, 1982, **66**, 492–495

Contrast sensitivity in diabetic subjects with and without retinopathy

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SUMMARY The clinical usefulness of the Arden grating test in assessing early abnormalities in retinal function of diabetics has been explored. Although the test revealed significant differences in constrast sensitivities between diabetics and normal persons, the large variances in the test scores of diabetics limit its use as a clinical tool for the screening of diabetic patients.

Diabetes is said to be associated with detectable alterations in colour perception before the development of ophthalmoscopically detectable retinopathy.[1] The Arden grating test[2] is claimed to detect disturbances of retinal integrative function even when acuity is normal. The test was used to assess whether it was of clinical value in detecting early abnormality in retinal function in diabetic subjects without retinopathy or in those with established retinopathy and whether it was useful in differentiating serious from not serious retinopathy.

Materials and methods

The test was carried out as described by Arden and Jacobson[2] except that standard artificial daylight was used (Verivide Cabinet, Leslie Hubble Ltd). Plates were presented at a standard distance of 57 cm and each eye was tested separately. The test was used in 80 normal subjects (age range 24 to 68, mean age 46, median age 45 years) and in 99 diabetic subjects (age range 27 to 70, mean age 47, median age 49 years). The ages of the 2 groups of subjects were comparable ($p > 0 \cdot 5$, Mann-Whitney nonparametric test). Forty-two of the diabetics had no detectable retinopathy on ophthalmoscopy. Twenty-two had background retinopathy, that is, scattered haemorrhages, microaneurysms, and a small number of hard exudates with retention of normal visual acuity. Twenty-nine patients had proliferative retinopathy as evidenced by disc or other new vessels. The visual acuities among patients with proliferative retinopathy ranged from 6/5 to 6/36 with a mean level of 6/9 and a median of 6/9. For analysis only one eye (the right) was used from each patient tested.

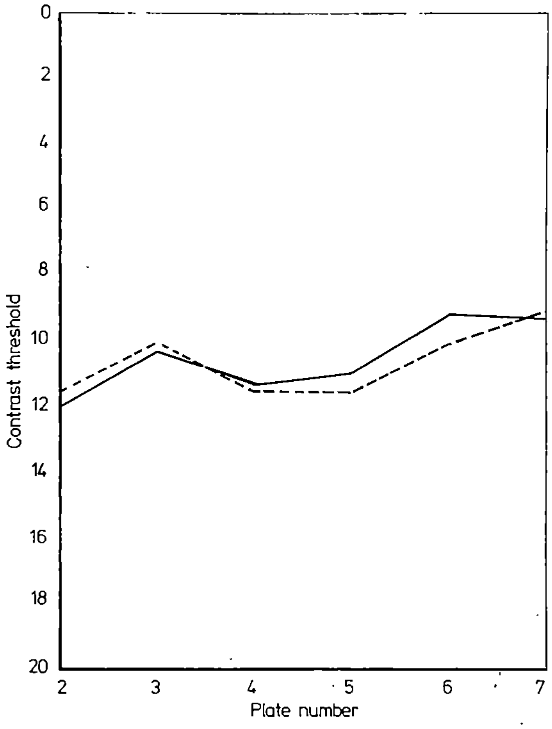

Fig. 1 *Mean contrast thresholds on Arden grating test for normal persons. (______) Our controls. (_ _ _ _ _) Arden and Jacobson normal persons.*

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Table 1 *A comparison of mean contrast thresholds for Arden and Jacobson's normals, our controls, all diabetics, and different groups of diabetic patients. Standard deviations are shown in brackets*

Plate	*2*	*3*	*4*	*5*	*6*	*7*
Arden's figures (SD=2)	11·50	10·00	11·50	11·50	10·00	9·00
Mean readings of our normal subjects	11·96 (2·27)	10·26 (1·89)	11·33 (2·08)	10·90 (1·98)	9·08 (2·25)	9·19 (2·56)
Mean reading of normal subjects	11·96 (2·27)	10·26 (1·89)	11·33 (2·08)	10·90 (1·98)	9·08 (2·25)	9·19 (2·56)
Mean reading of 99 diabetics	13·42 (3·72)	11·17 (3·39)	13·37 (3·54)	13·73 (3·99)	13·91 (6·39)	15·80 (7·31)
Normal	11·96 (2·27)	10·26 (1·89)	11·33 (2·08)	10·90 (1·98)	9·08 (2·25)	9·19 (2·56)
'No retinopathy' diabetic group	12·86 (4·03)	9·53 (2·99)	11·73 (3·32)	11·60 (3·50)	12·40 (7·28)	13·26 (8·07)
Normal controls	11·96 (2·27)	10·26 (1·89)	11·33 (2·08)	10·90 (1·98)	9·08 (2·25)	9·19 (2·56)
'Background' retinopathy group	13·60 (2·87)	12·00 (2·23)	13·33 (3·06)	13·13 (2·64)	12·66 (4·33)	14·86 (5·20)
'Proliferative' retinopathy group	13·80 (4·31)	12·00 (4·22)	15·06 (3·65)	16·46 (4·18)	16·66 (6·65)	19·26 (7·43)

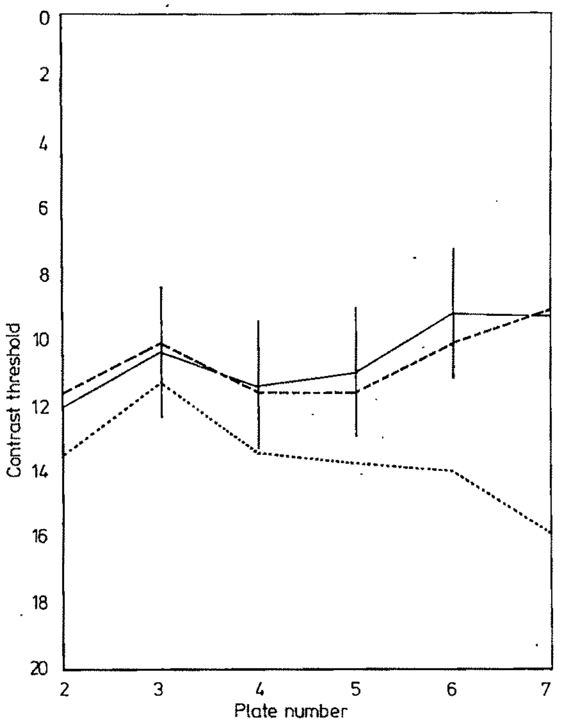

Fig. 2 *Mean contrast thresholds for: (______) Our normals. (_ _ _ _ _ _) Arden and Jacobson's normals. (. . . . . .) All diabetics. The vertical bars mark ±2 SD limits for our normals.*

Results

The mean contrast thresholds for normal and diabetic subjects for each of the 6 plates of differing spatial frequency used are shown in Table 1 together with the relevant standard deviations, as also are the mean normal values quoted by Arden and Jacobson.[2]

In general, for normal subjects our results for each plate were in agreement with those of Arden and Jacobson (Fig. 1) except for plates 5 and 6, where a significantly lower threshold was found for our normal subjects ($p<0·001$, each plate).

When the results for the 99 diabetic patients were compared with our normal results (or with those published by Arden and Jacobson), a significantly higher mean threshold was found for each plate (Fig. 2). When the results for our normal controls (Fig. 3) were compared with those from diabetic subjects without retinopathy, a significant increase in the threshold was found for the higher frequency plates 6 and 7 (whereas with Arden's control values a significant difference was also found with the low frequency plate number 2).

As would be expected, the results from our normal controls differed significantly from those obtained from patients with either background retinopathy or proliferative retinopathy (Fig. 4), as did the same results when Arden's control data were used.

When the various grades of retinopathy within the diabetic group were compared, the results were less clear-cut, though significant differences were found.

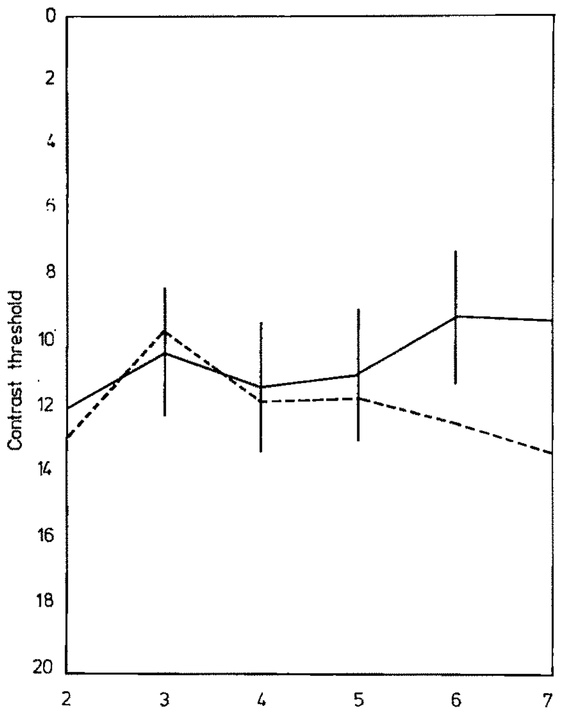

Fig. 3 *Mean contrast thresholds for: (______) Our normals. (_ _ _ _ _ _) 'No retinopathy' group. ± 2 SD limits for the normals are shown.*

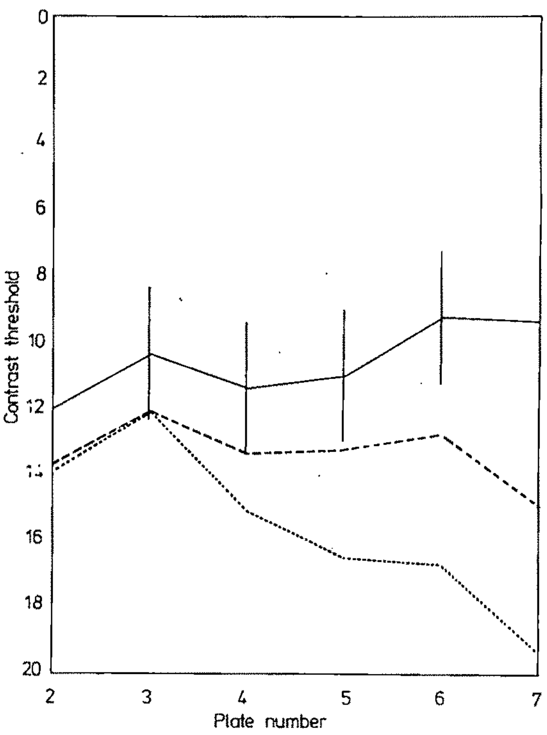

Fig. 4 *Mean contrast thresholds for: (______) Our normals. (_ _ _ _ _ _) 'Background' retinopathy group. (. . . . . .) 'Proliferative' retinopathy group. ± 2 SD limits for normals are shown.*

Thus the results for patients with diabetes but without retinopathy were significantly different in plates 3, 4, and 5 from those with background retinopathy and in all plates except plate 2 when compared with results from patients with proliferative retinopathy. Even when background retinopathy was compared with proliferative retinopathy, this latter group showed significantly increased thresholds for plates 5, 6, and 7 as compared with the former group. The results of the above comparisons are summarised in Fig. 5. The comparisons were made by a modified *t* test, applicable to cases with unequal variances.

It is worth noting that unlike the control group, in which the variance for each plate was similar (SD= 1·89 to 2·56), in all the diabetic groups the variances tended to be greater than in the controls, and particularly when higher frequency plates were used. An F test was used to assess whether the increased variance was significant, and significant values are marked with an asterisk in Fig. 6.

Discussion

Our results with the Arden grating test in normal subjects show a lower threshold for plates 5 and 6 (1·6 cycles/degree and 3·2 cycles/degree respectively) than those previously published by Arden and Jacobson[2] but are in agreement with figures recently published by Singh *et al.*[3] The results of the Arden grating test are to some degree age-related,[4] and the difference may reflect a different age composition in Arden and Jacobson's material and our own.

It is of interest that diabetic patients without retinopathy show increased thresholds at the higher spatial frequencies tested, which suggests that the functional deficit for these frequencies may precede ophthalmoscopically visible retinopathy.

Even within the group of diabetic patients increasing severity of retinopathy (background versus proliferative) was, as might be expected, associated with a decreased contrast sensitivity to grating patterns and an increasing variability in results, especially for plates of high frequency content.

Unfortunately the relatively large standard deviations in the groups affected by retinopathy resulted in considerable overlap between groups, so that the test was not found to be clinically useful in separating individual diabetic patients into serious or not serious

Plate	2	3	4	5	6	7	Comparison
				*	*		Normal Controls v. Arden Normals
	*	*	*	*	*	*	Arden Normals v. All Diabetics
	*				*	*	Arden Normals v. No Retinopathy
	*	*	*	*	*	*	Arden Normals v. Background Retinopathy
	*	*	*	*	*	*	Arden Normals v. Proliferative Retinopathy
	*	*	*	*	*	*	Normal Controls v. All Diabetics
					*	*	Normal Controls v. No Retinopathy
	*	*	*	*	*	*	Normal Controls v. Background Retinopathy
	*	*	*	*	*	*	Normal Controls v. Proliferative Retinopathy
		*	*	*			No Retinopathy v. Background Retinopathy
		*	*	*	*	*	No Retinopathy v. Proliferative Retinopathy
				*	*	*	Background Retinopathy v. Proliferative Retinopathy

Fig. 5 *Summary of the comparison of mean contrast thresholds. Differences significant at the level of at least p=0·05 are indicated by*.*

Plate	2	3	4	5	6	7	Comparison
						*	Normal Controls v. Arden Normals
	*	*	*	*	*	*	Arden Normals v. All Diabetics
	*	*	*	*	*	*	Arden Normals v. No Retinopathy
	*		*	*	*	*	Arden Normals v. Background Retinopathy
	*	*	*	*	*	*	Arden Normals v. Proliferative Retinopathy
	*	*	*	*	*	*	Normal Controls v. All Diabetics
	*	*	*	*	*	*	Normal Controls v. No Retinopathy
			*	*	*	*	Normal Controls v. Background Retinopathy
	*	*	*	*	*	*	Normal Controls v. Proliferative Retinopathy
					*	*	No Retinopathy v. Background Retinopathy
		*					No Retinopathy v. Proliferative Retinopathy
	*	*		*	*		Background Retinopathy v. Proliferative Retinopathy

Fig. 6 *Summary of the comparisons of the variances in contrast thresholds. Differences significant at the level of at least p=0·05 are indicated by*.*

categories of retinopathy. The test is, however, easily carried out and in conjunction with other findings may be useful in the assessment of the functional status of the eye in diabetic patients.

We thank Miss F. Maitland for secretarial assistance and Mr F. Addison for the preparation of the illustrations.

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British Journal of Ophthalmology, 1982, **66**, 496–499

Diabetic retinopathy and its relation to type of diabetes: review of a retinal clinic population

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SUMMARY A detailed survey was performed of 100 consecutive diabetic patients with severe retinopathy referred to a retinal clinic. They were classified as having either type 1 (insulin-dependent) or type 2 (noninsulin-dependent) diabetes. There were significant associations between type 1 diabetes and an initial diagnosis of proliferative retinopathy and between type 2 diabetes and an initial diagnosis of maculopathy. There was a significant association between male sex and proliferative retinopathy. Referral patterns to this clinic and the medical supervision of the patients are discussed.

The increasing recognition and provision of facilities for treating diabetic retinopathy in specialist centres have led to an expansion in the ophthalmological workload. While attention has focused on the treatment of established lesions with photocoagulation, emphasis should be placed on their prevention through the optimisation of blood glucose levels over prolonged periods of time. Evidence continues to accumulate that poor glycaemic control is the most important factor in the aetiology of diabetic retinopathy.[1 2]

Previous studies of the natural history of diabetic retinopathy and the grading of lesions have failed to take into consideration the clinicopathogenic heterogeneity of the diabetic syndromes. For example, the familiar textbook classification of diabetes into 'juvenile-onset' and 'maturity-onset' has now been largely abandoned by diabetologists. The currently used classification in the UK, which has also been adopted by the American Diabetic Association and the World Health Organisation,[3] divides the majority of diabetic patients into 2 groups: type 1 (insulin-dependent) and type 2 (noninsulin-dependent). Abundant evidence shows that these 2 polar forms of diabetes have a separate aetiopathogenesis.[4–6] The majority of type 1 diabetic patients develop the disease in childhood or adolescence, but it is by no means confined to this age group. Similar genetic and immunological features can be found in late-onset insulin-dependent cases. In contrast, type 2 diabetes does not seem to be due to an immune-mediated destruction of islet B cells. Although predominantly presenting in adult life, it is sometimes seen in young people. The aetiology of this type of disease remains largely unknown. Frequently patients with type 2 diabetes are treated with insulin to obtain better metabolic control. Thus, 'insulin-treated' patients are not necessarily insulin-dependent, and this should be borne in mind when classifying a group of patients according to their type of disease.

Kohner has suggested that there is an association between proliferative retinopathy and 'juvenile onset' diabetes and between diabetic maculopathy and 'maturity onset' diabetes.[7] Sorsby found a higher incidence rate of blindness due to diabetes in the 15–29 and 30–49 age groups in males than in females.[8] Caird *et al.* denied there was any association between sex and retinopathy, though their data from the Radcliffe Infirmary Diabetic Clinic show a male:female ratio of 51:25 in diabetic patients with retinopathy in the 10–29 age group.[9]

More recently Deckert *et al.*[10] suggested that male type 1 diabetic patients have a worse prognosis than females, and our own studies have shown a definite association between male sex and proliferative retinopathy in type 1 diabetes.[11] A recent study of reports of type 1 diabetic patients with severe

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microvascular disease, including both proliferative retinopathy and diabetic nephropathy, supported this association.[12]

This paper presents the results of a survey of consecutive diabetic patients with retinopathy referred to a specialist retinal clinic and examines the relationship between the type of retinal lesion and the type of diabetes. Referral patterns and the medical supervision of the patients were assessed.

Subjects and methods

The study was based on diabetic patients referred to the retinal clinic at St Bartholomew's Hospital. They were classified as having either type 1 (insulin-dependent) or type 2 (noninsulin-dependent) diabetes according to the following features of their clinical history: insulin dependence or independence, age at onset, history of ketosis, body weight at diagnosis, and familial type of diabetes. Those patients with either lens opacities or only minimal background retinopathy—that is, less than 5 microaneurysms and without macular involvement or retinal oedema—were excluded. The resultant 100 consecutive patients with severe retinopathy were considered in the analysis.

The retinae were examined by a consultant ophthalmologist (R.A.F.W. or J.H.D.) by direct and indirect ophthalmoscopy, colour photography, and in most cases fluorescein angiography. The subjects were then classified according to their retinal diagnosis at initial presentation to our clinic or to the referring ophthalmologist as having (*a*) proliferative retinopathy, (*b*) diabetic maculopathy, or (*c*) severe widespread background diabetic retinopathy. One case was found to have a disciform degeneration as the cause of severe visual loss. The current age, age at diagnoses of diabetes and retinopathy, known duration of diabetes, and interval between the diagnoses of diabetes and retinopathy were noted in each subject. They were asked about the frequency of home testing of urine or blood for glucose and about the frequency and type of medical follow-up. The source of referral to the clinic was recorded.

Results

The current age, age at diagnosis of diabetes, and known diabetes duration are shown in Table 1. As would be expected, the type 2 diabetic patients were older, had a later age of onset of diabetes but a shorter known duration of diabetes than the type 1 diabetics (all differences $p<0\cdot0001$, Student's unpaired *t* test).

Table 1 *Mean age, age at diagnosis of diabetes, and known duration of diabetes*

	Type 1 diabetes (n=57)	*Type 2 diabetes (n=43)*
Current age	45±13 (21–73)	62±8 (43–81)
Age at diagnosis of diabetes	203±13 (1–49)	51±11 (27–79)
Known duration of diabetes	25±9 (9–49)	11±8 (2–26)

Results expressed in years as mean±SD (range).

Out of 100 consecutive diabetic subjects with sight-threatening lesions 57 had type 1 (insulin-dependent) and 43 type 2 (noninsulin-dependent) diabetes. Of the latter group 9 had failed to obtain adequate control on their initial treatment with diet or oral hypoglycaemic agents and subsequently were receiving insulin.

There was an excess of males in the type 1 diabetic patients (M:F=41:16) in contrast with the equal sex ratio in the type 2 diabetic patients (M:F=22:21), though this difference was not statistically significant (χ^2 with Yates's correction 3·69, $p=0\cdot055$).

There was a strongly significant association between type 1 diabetes and proliferative retinopathy and type 2 diabetes and diabetic maculopathy (corrected χ^2 24·5, $p<0\cdot00001$), as shown in Table 2. In addition Table 3 shows the significant association found between male sex and proliferative retinopathy ($\chi^2=7\cdot54$, $p=0\cdot0118$).

Table 4 shows the known duration of diabetes at the initial presentation with retinopathy. The subjects with type 2 diabetes had a shorter known duration of diabetes at the onset of retinopathy than those with type 1 diabetes, whether considered as a whole ($p<0\cdot0001$), with proliferative retinopathy ($p<0\cdot0001$), or with maculopathy ($p<0\cdot02$, Student's *t* test). The difference for severe background retinopathy was not significant. Within the 2 diabetic groups the differences in the intervals before retinopathy for the 3 retinal diagnoses were not statistically significant.

The age at diagnosis of retinopathy is shown in

Table 2 *Relationship of retinal diagnosis to type of diabetes*

	Number of patients	
	Type 1 diabetes	*Type 2 diabetes*
Proliferative retinopathy	44	12
Maculopathy	7	25
Severe background retinopathy	6	5
Disciform degeneration	0	1
Total	57	43

$\chi^2=24\cdot5$, $p<0\cdot00001$.

Table 3 *Sex distribution in relation to retinal diagnosis*

	Male	*Female*
Proliferative retinopathy	41	15
Maculopathy	14	18

$\chi^2=7{\cdot}54$, $0{\cdot}01>p>0{\cdot}001$.

Table 4 *Known duration of diabetes at initial diagnosis of retinopathy*

	Type 1 diabetes	*Type 2 diabetes*	*Combined*
Proliferative retinopathy	19±8 (1–34)	7±8 (0–23)	16±9
Maculopathy	20±2 (7–41)	7±7 (0–20)	10±10
Severe background retinopathy	19±3 (15–22)	11±9 (4–26)	15±7
Combined	19±8	8±7	

Results expressed in years as mean±SD (range).

Table 5 *Age at diagnosis of retinopathy*

	Type 1 diabetes	*Type 2 diabetes*	*Combined*
Proliferative retinopathy	38±12 (19–69)	52±9 (39–67)	41±13
Maculopathy	38±17 (20–59)	61±7 (51–76)	56±13
Severe background retinopathy	46±17 (24–66)	59±5 (54–66)	52±14
Combined	39±13	58±8	

Results expressed in years as mean±SD (range).

Table 5. The 3 retinal diagnoses occurred at a similar age in each type of diabetes. However, in the type 2 diabetic patients proliferative retinopathy occurred at a significantly earlier age than maculopathy ($p<0{\cdot}01$).

The patients were referred from various sources: 39 were from other ophthalmic consultants, 35 from the diabetic clinics of this hospital group, 16 from other diabetic clinics, 7 from general practitioners, one each from a neurologist and a general surgeon, and one patient who worked in this hospital referred herself.

Of the 100 patients 85 tested themselves for glycosuria. The average number of tests (±SD) performed was 7±6 per week. Four of these patients also monitored their blood glucose level. However, the remaining 15 did not monitor their diabetes at all.

Sixty-nine patients regularly and 7 irregularly attended a diabetic clinic. Three were supervised regularly and one irregularly by a general practitioner. Two regularly attended a general physician. Eighteen (10 insulin-dependent, 8 non-insulin-dependent) were not receiving any supervision of their diabetes despite severe retinopathy threatening their sight. Reasons given for this lack of supervision included having been discharged from a diabetic clinic, believing that medical supervision was no longer necessary, and dissatisfaction with the diabetic clinic either due to a long waiting time or seeing a different doctor on each occasion.

Discussion

Surprisingly, there is virtually no documented evidence on the association between the major forms of diabetic retinopathy with the type of diabetes. The present results confirm that proliferative retinopathy is significantly associated with type 1 diabetes and diabetic maculopathy with type 2 diabetes. Type 1 diabetes usually but not always presents at a younger age than type 2 diabetes, and thus the patients with type 1 diabetes had a lower age of onset of diabetes and of retinopathy than those with type 2 diabetes. The reason for this segregation of retinal lesion with type of diabetic syndrome is unknown. If hyperglycaemia is the common factor leading to retinopathy, it would be expected that the type of diabetes would be irrelevant.

It is possible that the excursions in blood glucose level are wider and more erratic in type 1 than in type 2 diabetes, and this together with other more severe metabolic deviations may influence the retinal pathology. However, the older age of the patients with type 2 diabetes may itself be important, as macular disease in general is more common in the older age group. The study also showed that proliferative and macular lesions may each occur in both major forms of diabetes. Indeed in the case of localised macular disease new vessels may arise later, or the background changes may become more widespread and severe.

This study confirms the association between male sex and proliferative retinopathy in type 1 diabetes.[11] Children with type 1 diabetes show a slight but definite male preponderance,[13] but why male patients tend to fare more badly is not clear. Hormonal, genetic, social, or psychological factors may contribute to this increased risk. This sex difference may have been masked in previous studies when patients with different types of disease were considered together. The majority of diabetic patients have the type 2 variety, and in this older group females predominate. This may account for the excess of females among the registered blind.

The duration of diabetes at the presentation with retinopathy was longer in the patients with type 1 diabetes than in those with type 2 diabetes. This difference may be artificial to some extent, as the type 2 diabetic patients probably had undetected hyperglycaemia for longer than their known duration of disease. It is of interest that the duration of diabetes at the presentation with retinopathy was not significantly affected by the type of retinal diagnosis within each group. Thus proliferative retinopathy does not appear earlier in the course of the disease than maculopathy. Factors in the individual patient must determine which retinal lesion develops.

It is disturbing that 18% of these patients were receiving no medical supervision of their diabetes, and 15% were not assessing their diabetic control.

In conclusion we suggest that close co-operation between the diabetic patient and physician may minimise the risk of complications, and co-operation between the physician and ophthalmologist may prevent their progression.

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British Journal of Ophthalmology, 1982, **66**, 500–505

Refractive change in hyperglycaemia: hyperopia, not myopia

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SUMMARY Sudden changes in refraction are a well recognised feature of hyperglycaemia. A tendency towards myopia has always been associated with elevations in blood glucose. Twelve diabetic patients were found to have experienced such refractive changes. Review of their records demonstrates that hyperglycaemia produces hyperopia. A theoretical mechanism for this phenomenon is discussed.

The occurrence of transitory refractive changes in diabetic patients has been recognised since 1873.[1] However, since that initial observation there have been conflicting reports of the nature of the changes and the reasons for them.

After reviewing 3 of his own cases and 45 cases from the literature Duke-Elder in 1925 concluded that hyperopia is less common than myopia and that 'the refractive power of the eye tends to vary directly as the sugar content of the blood; that is, there is a tendency to hypermetropia with decreased sugar, with increased sugar to myopia.'[2] Both Bellows and Roberts agreed with this association but maintained that diabetic myopia is less common than diabetic hyperopia.[3 4] Granström reported refractive change occurring as an initial symptom in 34% of diabetics and as an asymptomatic change in another 47%.[5]

It has been said that hyperopia seems not to occur as an initial phenomenon in diabetes but to follow myopic change,[6] and many authors have correlated the development of hyperopia—or the reversal of myopia—with a falling blood sugar, usually associated with treatment of hyperglycaemia and especially if this is rapid.[2 4 7–12] It has also been suggested that hyperopic change in diabetes occurs almost exclusively in those patients receiving insulin.[13]

In 1956 there was a report by Rosen of a single case of hyperopia due to hyperglycaemia.[14] More recently Duke-Elder's rule has been refuted by Planten's study of 23 patients of whom only 2 became myopic with hyperglycaemia, the remainder all showing transient hyperopia.[15] Feinblum presented 100 cases in which the initial diagnosis of diabetes was based on a sudden refractive change, hyperglycaemia always being associated with hyperopia.[16]

Most authors accept Duke-Elder's theory that refractive changes in diabetes are due to alterations in the power of the lens because of osmotic interactions between the lens and aqueous.[2 3 6 7 10 17 18] Myopia with hyperglycaemia was then explained as being due to osmotic hydration of the lens due to salt retention.[2 3] Rosen accounted for hyperopia with hyperglycaemia by assuming that hydration must involve the nucleus as well.[14] Meanwhile Granström suggested that the hydration would occur when the blood sugar was *decreased*, and that involvement of the nucleus preferentially would account for the hyperopia developing at that time.[5]

Later writers have suggested that intralenticular osmotic pressure increases during hyperglycaemia as glucose and its metabolic products, especially those derived from the sorbitol pathway, accumulate within the lens.[7 13 19 20] The resultant influx of water has been used to explain either a myopic or a hyperopic change, according to whether shape or refractive index is considered more important in determining overall refractive power.[19–21]

For this paper we have reviewed the records of all of the diabetics seen by D.G.V. in his clinic from 1959 to 1981 who are known to have had a sudden visual change in association with hyperglycaemia. Thirteen such instances in 12 diabetic patients are reported. Every case showed transient hyperopia developing prior to the diagnosis of diabetes or soon after treatment was started, or in some cases at the time of an acute disturbance in the course of their disease. *There was no evidence of any association between hyperglycaemia and myopia.* A possible mechanism

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for the development of hyperopia involving the sorbitol pathway of metabolism is discussed.

Case reports

GROUP A

Patient 1, a 65-year-old woman, was admitted to hospital on 11 September 1973 with a 4-week history of weight loss, thirst, vaginitis, and weakness. She had also had blurring of vision, both near and distance, for one week. She was diagnosed as having diabetes. After control had been established she was discharged from hospital on insulin therapy.

She was seen in the clinic on 12 October, at which time her vision was still blurred. There had been no apparent improvement in her visual status. Visual acuity was 20/200(6/60) in each eye with her current prescription (OD +1·50=+1·00×20, OS +1·50=+0·50×155). Best corrected visual acuity was 20/20 (6/6) with OD +3·25=+1·00×20, OS +3·75=+0·50 ×155. Temporary +1·50 clips were recommended.

Within 5 weeks of this examination the right eye had returned to its previous refractive error of +1·50, but the left only settled to +1·75 after another 5 weeks.

Four other cases (patients 2–5) were seen in which the appearance of hyperopic refractive changes predated the diagnosis of diabetes. In 2 of these it is definitely known that hyperopia also preceded the development of other diabetic symptoms.

GROUP B

Patient 6, a 35-year-old woman, was seen in hospital on 18 May 1967 at the request of her internist. She had been admitted on 8 May for stabilisation of recently diagnosed diabetes mellitus. There was a history of polyuria, polydipsia, fatigue, and vaginal pruritus, and she had been initially treated for 3 days with tolbutamide. Because oral therapy failed to control the blood sugar, which was 440 mg/dl (24 mmol/l) on the day of admission insulin therapy was instituted at that time.

The patient had had no visual symptoms until the day after her admission, when she noticed blurring of near vision progressing to involve distance vision 4 days later. Her vision remained the same until after the initial consultation, but meanwhile she noticed that she could see much better, both near and distance, with some +2·50 cheap reading glasses. Her normal prescription was −0·50=+0·50×90 OU.

Examination at the time of the initial consultation revealed an uncorrected visual acuity of approximately 20/200 (6/60) in each eye, corrected to approximately 20/40 (6/12) with the reading glasses. At a more formal examination on 29 May, after her discharge, the patient said that her vision had started to improve 4 days previously, so that she was no longer able to see at a distance with the +2·50 reading glasses and she could read without glasses. Refraction then disclosed a +1·25 error in each eye with corrected visual acuity of OD 20/25 (6/7·5) and OS 20/30 (6/9). Further improvement did occur, and the refractive error settled at +0·25 in the right eye and +0·50 in the left by November 1967.

Patient 7, a 64-year-old man, was being followed up at the clinic after a retinal detachment in 1955. The last refraction before the onset of diabetes was in June 1980, when corrected visual acuity was 20/30 (6/9) with −4·75=+1·00×170 in the right eye and −4·75=+1·00×30 in the left.

In December 1980 he suddenly developed severe polydipsia and polyuria. On 15 December investigation by his internist showed a full blood sugar value of 350 mg/dl (19 mmol/l). Chlorpropamide, one tablet per day, was started. Although the patient discontinued this treatment within a few days because of side effects, frequent blood sugar estimations continued to show improvement.

About 2 weeks after initiation of treatment the patient noticed a sudden change in his vision in that he could no longer see street signs while driving unless he took his glasses off. Examination by an optometrist on 8 January 1981 showed best visual acuity of 20/25 (6/7·5) with corrections of −1·75 in each eye. Referral back to an ophthalmologist was advised. The patient's prediabetic refractive error was found to have returned on 27 February 1981.

One other patient (patient 8) gave a similar history of suddenly being able to see in the distance without glasses, despite previously being myopic, about 2 weeks after starting oral medication for newly diagnosed diabetes.

GROUP C

Patient 9, a 36-year-old diabetic woman had been taking chlorpropamide for 5 years when she developed influenza in January 1972, and her diabetes went out of control. By 8 February her full blood sugar had risen to 350 mg/dl (19 mmol/l) and she was advised to start insulin therapy on 19 February. Until that time she had had no visual symptoms since the onset of her diabetes in 1967, but within 3 hours of the first injection of 10 units of regular insulin she noticed blurring of vision in both eyes. She could not see with her glasses (OD −3·25=+0·25×135, OS −3·75=+1·25×40), but she could see near without them. A formal refraction on 22 February showed visual acuity of 20/200 (6/60) OU with her present glasses, OD 20/80 (6/24) and OS 20/60 (6/18) without correction, and 20/20 (6/6) with a −1·50 sphere in each eye. Temporary +1·50 were recommended.

An increase in the dosage of insulin led to gradual lowering of the blood sugar, followed later by a reversal of the refractive change. In January 1973 the refractive errors had returned to −3·25 in the right eye and −3·50 in the left with the same astigmatic corrections.

Three other patients (patients 10–12) were recorded as experiencing hyperopic refractive changes in association with exacerbations of diabetes already under treatment. Patient 11 had two similar episodes in the space of 2½ years. In all cases the disturbance of vision occurred soon after treatment was altered to control hyperglycaemia.

In Table 1 are listed the actual values of the refractions for each patient before the hyperglycaemic episode and at the time of the maximum measured change. All refractions were carried out by D.G.V. There was no apparent effect on the astigmatic corrections, and so these are not shown. The peak blood sugar value is also recorded in each case, but it is not possible to make any valid correlation between this and the measured refractive changes because of differences in the timing of these measurements.

Discussion

Although many textbooks of ophthalmology discuss temporary refractive changes as a feature of diabetes mellitus, the nature of such changes has not been defined. Most authors still adhere to Duke-Elder's concept of myopia associated with hyperglycaemia, and only a few report the possibility of hyperopia under such circumstances.[17 22 23]

This paper presents 13 instances in which hyperglycaemia produced either hyperopia or a reversal of myopia. Our cases failed to support the view that elevations of blood glucose in diabetes are accompanied by a tendency towards myopia. The patients' own accounts of their visual changes as well as objective evidence obtained by clinical refraction directly contradict that opinion. Other recent publications lend support to our finding,[15 16] but the series reported here is the first in the ophthalmological literature that demonstrates an association between hyperglycaemia and hyperopia in a substantial number of well-studied cases.

In this series the age range of cases is from 27 to 72 years, with most of the patients over 50. Although

Table 1 *Hyperglycaemia-induced hyperopia in 12 diabetic patients*

Patient	*Age*	*Sex*	*Refractions*		*Overall refractive change*	*Peak full blood sugar mg/dl*
			Before hyperglycaemia	*Maximum change*		
Group A: Prior to diagnosis						
1	65	F	OD +1·50	+3·25	+1·75	550
			OS +1·50	+3·75	+2·25	
2	57	F	OD +2·50	+3·25	+0·75	315
			OS +2·00	+3·00	+1·00	
3	63	M	OD −0·75	+0·50	+1·25	360
			OS −3·50	−0·50	+3·00	
4	72	F	OD Plano	+1·75	+1·75	300
			OS Plano	+1·25	+1·25	
5	27	F	OD −0·25	NA	NA	560
			OS Plano	NA	NA	
Group B: Soon after treatment						
6	35	F	OD −0·50	+1·25	+1·75	440
			OS −0·50	+1·25	+1·75	
7	64	M	OD −4·75	−1·75	+3·00	350
			OS −4·75	−1·75	+3·00	
8	63	M	OD −3·50	−1·00	+2·50	NA
			OS −3·00	−0·50	+2·50	
Group C: Previously treated diabetes						
9	36	F	OD −3·25	−1·50	+1·75	350
			OS −3·75	−1·50	+2·25	
10	62	F	OD+ 1·25	+3·00	+1·75	345
			OS +1·50	+3·00	+1·50	
11 (i)	52	F	OD −1·00	+1·50	+2·50	448
			OS −2·00	+1·25	+3·25	
11 (ii)	54	F	OD −0·75	+1·50	+2·25	576
			OS −1·50	+1·50	+3·00	
12	65	F	OD +1·25	+3·75	+2·50	318
			OS +1·25	+3·50	+2·25	

NA=not available.
SI conversion=mg/dl×0·0555=mmol/l.

this does not establish an association with advancing years, it does show that this effect is not necessarily confined to younger diabetics, as claimed by Himsworth.[24] Furthermore of the cases presenting with visual changes near the time of the initial diagnosis of diabetes 4 were treated with insulin and 4 with oral medication. There was a good correlation between the peak full blood sugar value and the treatment method used. Thus it would seem that hyperopia is not necessarily commoner in patients who have severe metabolic disturbance at the onset, or those treated with insulin.

The development of refractive abnormalities in response to hyperglycaemia is characterised by rapid onset followed by prolonged regression.[2 7 11 13] In all our cases the hyperopic change occurred suddenly, never taking more than a few hours to appear. Return to the previous refractive state often required weeks, depending on how rapidly and reliably the blood glucose level was controlled. Patients adequately treated with insulin improved steadily over a period of 6 to 10 weeks, whereas those receiving oral medication took as long as 20 weeks. In one case (patient 9) a year elapsed before suitable refraction was re-established, probably due in large part to failure to achieve satisfactory diabetic control. Previous investigators have generally believed refractive changes in diabetes, whether they be myopic or hyperopic, to be completely reversible. Two of our 12 cases (patients 4 and 6) failed to return to within one dioptre of their prediabetic refraction in either eye even with well-documented satisfactory control of diabetes. It has been suggested that this phenomenon may be due to reliance on quantitative urine analysis, in patients with high renal thresholds, rather than regular monitoring of blood glucose.[16] However, it is known that—at least in the case of patient 4—frequent blood glucose examinations were being done.

The magnitude of the measured refractive changes in this series ranges from 0·75 to 3·25 dioptres. Although these may be underestimates because of delay between the onset of the refractive change and the time of the next formal refraction, including when subjective visual improvement had been noticed, the results are the same as those given by other authors.[6 11 12 14–16] In all cases both eyes were affected, and in only one instance (patient 3) was there a difference of more than 0·75 dioptres between the changes in the 2 eyes. This may have been related to the great disparity in this patient's prediabetic refraction. The sex distribution in this study shows a bias (3:1) towards women.

As has been mentioned, several mechanisms have been proposed to explain temporary abnormalities of refraction in diabetes, often with only apparently minor differences according to the nature of the changes observed. Duke-Elder in 1925 extensively reviewed the ideas current at that time and set forth the 2 concepts of a lenticular origin and an osmotic basis for this phenomenon.[2] He listed 6 major reasons for implicating the lens, of which Elschnig's observations in unilateral aphakia are the most persuasive, and provided an elaborate exposition of the possible role of osmotic forces, which established the concept without truly explaining the mechanism. His idea of a decrease in the osmotic pressure of the aqueous in the face of hyperglycaemia, with consequent hydration of the cortical layers of the lens, has been reiterated by other authors. However, recent physiological evidence is to the contrary (see below). Caird, Pirie, and Ramsell in 1969[13] suggested that the osmotically active substances involved may actually be formed within the lens, and this theory has subsequently attracted a number of supporters.[7 19 20 25]

By 1965 it had been reported that the sorbitol pathway is active in the lenses of both humans and animals and that in diabetes the metabolites of the pathway are abnormally high.[26–29] Incrimination of polyol production in the development of cataracts in galactosaemia led to an intensive search for a similar mechanism in diabetic cataracts.[30–32] Furthermore, since it is known that the metabolites can accumulate to significant levels within a few hours, similar mechanisms have been considered as the basis of more acute changes in the lens.[25 33] It is known that there is a direct correlation between the level of glucose in the aqueous and that in the blood under normal or hyperglycaemic conditions.[34] However, the corresponding relationship between the lens and the aqueous is more complex.

Experimental data suggest that glucose diffuses into the lens and permeates the small extracellular space, which accounts for 5–10% of the lens volume, and that at normal levels of glucose in the blood and aqueous humour the rate of glucose utilisation by the lens fibre cells is equal to its rate of entry, so that the cells are essentially glucose-free.[34 35] However, if glucose levels in the surrounding medium are increased, lens fibres seem to accumulate glucose, and more especially—because of the apparent diversion of this substrate into the sorbitol pathway—the metabolites sorbitol and fructose.[36] The reason is probably saturation of the enzyme hexokinase, the starting point of the glycolytic and pentose phosphate pathways in combination with the markedly higher Km of aldose reductase, the first enzyme of the sorbitol pathway.[37] The net result is an accumulation of fructose and sorbitol, both of which penetrate lens membranes poorly and are further metabolised to only a limited extent. Since their concentrations may not be matched in the aqueous humour, an osmotic imbalance may develop, with the consequent imbibition of water. Experiments with human lenses have shown that lens tissue is capable of forming sufficiently high levels of sorbitol with 24 hours of continuous hyperglycaemia, to lead to a hypertonic state.[37] Hyperglycaemia-induced refractive changes have been prevented in rabbits by aldose reductase inhibitors, although similar work in human subjects has yet to be published.[25 33]

There has been much debate about which part of the lens is responsible for the refractive changes during hyperglycaemia. Since reliance still must be placed on models to explain the physiological optics of the lens, and since little is known about the applicability of such studies to lenticular function under pathological conditions, it is difficult to choose among the proposed hypotheses. Studies involving direct examination of human lenses in vivo during hyperglycaemia are scarce. Huggert observed 'blurring of the inner surface of the lens' on slit-lamp examination in patients with transitory diabetic hyperopia and suggested that there may have been some swelling anterior to the nucleus.[38] More rapid changes were observed by Vere and Verel, who ascribed dimming of the red reflex with hyperglycaemia to transient opacity in the anterior lens.[39] They discounted hyperopic change as a possible alternative cause—although shown to have a similar effect—because of Duke-Elder's association of hyperglycaemia with myopia. Following up their personal studies published in 1975, Planten *et al.*, with the aid of ultrasonic A scans, failed to reveal any difference in the optic parameters of the lens and its position in the eye during and after episodes of hyperopia in diabetes.[21] Their conclusion, supported by mathematical evidence of its feasibility, was that changes of the refractive indices in the various layers of the lens are the cause of the hyperopia developing in diabetes, rather than an alteration in the size of the lens. Subsequently they showed that such changes can be visualised by the appearance of refractive surfaces in the lenticular cortex.[40] It would thus appear that a decrease in the refractive indices within the anterior portions of the lens might produce the hyperopia associated with hyperglycaemia. It is tempting to speculate that an osmotic effect due to the accumulation of sorbitol and fructose could account for these findings, since aldose reductase is known to be principally located in the lens epithelium and cortex.[37]

Before accepting a theory it is necessary not only to prove its own merit but also to explain why other theories are either wrong or not applicable. A review of the published series shows that many writers on this subject had no knowledge of their subjects' refractive error before the onset of hyperglycaemia and that many analysed the refractive changes only after treatment had been started. It is of interest that a number of our cases show a relationship with the onset of treatment and not necessarily with the development of hyperglycaemia per se. Hyperopic change occurs in these instances as a possible consequence of the reduction of the blood sugar after a period of hyperglycaemia. Analysis of the first case cited in Duke-Elder's original paper shows an identical happening. Duke-Elder was also able to demonstrate that subsequent elevation of blood glucose resulted in a reversal of this change, causing only slight myopia—in comparison with the patient's subsequently established normal refraction—when the blood sugar was grossly elevated. The findings convinced Duke-Elder that there must be a direct association between myopia and hyperglycaemia, but it would appear more likely that there is some link between hyperglycaemia and hyperopia, which is modulated by the prevailing blood glucose level. It is logical to assume that, if the change in refraction depends on an osmotic force acting from within the lens, then any osmotically active substance—such as glucose—in high concentration in the aqueous may be able to counteract this force. Imbibition of water into the lens could then not occur until the extralenticular glucose concentration had been reduced. Thus a balance can be visualised between the amount of accumulated sorbitol or fructose and the extralenticular glucose concentration that controls the movement of water into and out of the lens. A grossly elevated glucose level may produce rapid accumulation of polyol metabolites, but these cannot exert any osmotic effect without a reduction in the sugar level; whereas in the presence of a relatively small elevation of glucose over a longer period of time a sufficient accumulation of metabolites may have an overall osmotic effect. Alloxan-induced diabetes in animals has been noted to produce refractive changes, which are always hyperopic even in the presence of elevated blood glucose.[13] This fact may be related to the much greater activity of the enzymes of the sorbitol pathway in the lenses of such animals.[37]

Further extrapolation of this mechanism suggests that the few instances in which myopia does occur, with severe metabolic disturbance, would be due to an osmotic dehydration of the lens because of rapid elevation in extralenticular glucose in advance of the accumulation of polyol metabolites. This would then be short-lived, hyperopia developing once the metabolites have accumulated and the extralenticular glucose level has been reduced.

Whether an increase in the metabolism of glucose via the sorbitol pathway with consequent accumulation of polyol metabolites does account for the refractive changes produced by hyperglycaemia is not conclusively established. Such a mechanism does provide an explanation for many of the features of these refractive changes, especially their time of onset and regression. Furthermore it would establish a direct link with current ideas concerning cataractogenesis in diabetes. The most important result of the study offered here, however, is that hyperopia is the refractive change associated with hyperglycaemia.

We are grateful to James Ransom, PhD, for his editorial advice and John H. Sullivan, MD, for his help in compiling this paper. Nancy Kettman kindly typed the manuscript.

Paul Riordan Eva was a student-fellow of the Francis I. Proctor Foundation for Research in Ophthalmology, University of California, San Francisco. Support for this study was provided by the Sight Conservation Research Center, San Jose, and the Alta California Research Foundation, San Francisco.

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British Journal of Ophthalmology, 1982, **66**, 506–508

Acyclovir and trifluorothymidine in herpetic keratitis: a multicentre trial

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SUMMARY A randomised double blind study was performed on 59 patients with dendritic herpetic keratitis treated with 3% acyclovir or 2% trifluorothymidine ointment. Both drugs were highly effective and gave 87% (ACV) and 82% (TFT) success rates. Punctate keratopathy occurred in 70% of the patients, but serious side effects were not observed.

Since the introduction of idoxuridine (IDU) as an antiviral drug for the treatment of herpetic keratitis more potent drugs have become available. Arabinoside adenine and trifluorothymidine (TFT) are both effective and relatively nontoxic alternatives widely used in the management of herpetic disease.[1] Acyclovir (ACV) (9-(2-hydroxyethoxymethyl) guanine)[2] and (E)-5(2-bromovinyl)-2′ deoxyuridine),[3] recently developed antiviral compounds with potent inhibitory activity against herpes simplex DNA polymerase, do not inhibit normal human cell DNA polymerase.

For a comparative study we selected 2 of the antiviral drugs which we considered to be the most potent —acyclovir and trifluorothymidine.[4 5]

Material and methods

Fifty-nine patients with dendritic keratitis were studied. Patients with stromal keratitis and patients treated by antiviral agents and/or corticosteroids prior to referral were excluded. In a randomised double-blind study we used 3% acyclovir and 2% trifluorothymidine ointment, both specially prepared for this trial and packed in identical tubes obtained through the kind co-operation of Wellcome Laboratories (England) and Dr Gerhard Mann, Hamburg (FRG), respectively. The ointment was prescribed 5 times daily. Cycloplegics were given for intraocular irritation.

After healing was complete the treatment was continued for 7 days. It was discontinued if after 7 days no therapeutic effect was observed or if after 14 days the keratitis had not healed completely.

The keratitis was considered to be cured when the lesion no longer stained with fluorescein 10–20%. Slit-lamp examination was performed in the outpatient department, usually every day so as to assess the exact day of healing. At all examinations colour slides were made of the cornea at 2× linear magnification without staining and after 10–20% fluorescein staining with a blue filter in front of the electronic flash. The findings were recorded on a proforma specially designed for this study. The results of a preliminary study have been published elsewhere[6]; this paper deals with the final results in 59 patients with herpetic dendritic keratitis.

Results

Thirty-one patients were treated with ACV and 28 with TFT. The groups were well matched in terms of sex and age, and there was no significant difference between them (Table 1). Most of the patients in both

Table 1 *Distribution according to sex and age of acyclovir and trifluorothymidine treated patients*

	ACV	*TFT*	
Number of patients entered	31	28	
Sex:			
male	22	12	No significant difference $\chi^2=3{\cdot}21$ p=>0·05
female	9	16	
Age:			
younger than 50 years	16	12	No significant difference
50 years and older	15	17	

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Table 2 *Duration of symptoms at presentation*

	ACV	*TFT*
Up to 7 days	26	24
8–14 days	3	4
15–21 days	2	0

Table 3 *Duration of treatment in days*

	ACV	*TFT*
Average	6·3	7·1
Standard deviation	2·4	4·0
Total duration of treatment	15·1	15·8

groups had had their eye complaints for less than 7 days (Table 2).

The results are summarised in Fig. 1, which shows that in 27 out of 31 ACV-treated patients and 23 out of 28 TFT-treated patients the keratitis had healed after 2 weeks of treatment. The average duration required for healing of the keratitis was 6·3 days in the ACV series and 7·0 days in the TFT series (Table 3). The difference was not statistically significant. Nor was there any statistical correlation between the duration of the complaints before treatment and the healing time after antiviral treatment was started.

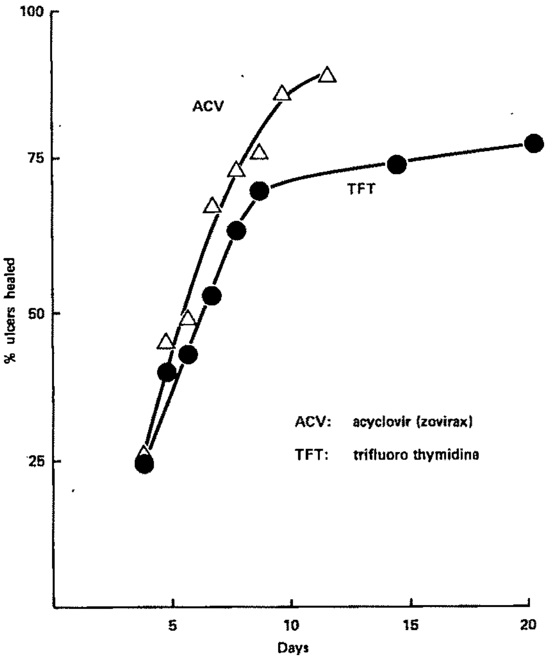

Fig. 1 *Cumulative frequency distribution of time taken to heal dendritic keratitis in 27 acyclovir and 23 trifluorothymidine treated patients.*

The most frequently observed side effect was superficial punctate keratopathy, showing fluorescein staining outside the area of the herpetic lesions. This occurred in about 70% of patients in both groups, with an average duration of slightly more than one week. In both groups a few patients complained of a stinging sensation after application of the ointment, but extensive conjunctival hyperaemia was seen in only 3 patients receiving TFT, and it disappeared a few days after discontinuation of the treatment. In neither groups were there short-term recurrences of herpetic keratitis.

Discussion

There is ample evidence that TFT is an effective antiviral agent, with up to 95% healing of dendritic herpetic keratitis.[4 5] This induced us to test the more recently developed ACV in a double-blind study with TFT. The results showed that both compounds are highly effective, and there was no statistical difference between them. Our results of ACV treatment in patients agree with the favourable results of experiments in rabbits.[1 7–11] Other results of clinical trials with 3% ACV ointment in dendritic or geographic herpetic keratitis are also favourable and agree with our results.[12–15] The average healing time in our series of ACV-treated patients was 6·3 days, which is longer than the 4·4 days in the series of Collum *et al.*[13]

In our preliminary study 20 ACV-treated patients had healed within 10 days,[6] but in the present series 4 out of the 31 eyes failed to heal. In previous studies, totalling 84 ACV-treated eyes, the keratitis in all eyes responded well to the treatment and healed.[13–15] The lack of efficacy which we observed may have been caused by resistance against herpes virus strains comparable to that of strains refractory to TFT. But this cannot be proved because inadequate treatment could be the explanation in patients treated on an outpatients basis.

As this was a multicentre study, special care was taken to make a strict protocol and a proforma for each patient. Moreover, regular, often daily, photographic recording was performed after 20% fluorescein staining. Joint sessions for evaluation helped us to detect even the slightest epithelial lesions. This accounts for the high percentage of punctate keratopathy (about 70%) observed in both ACV and TFT treated patients, as the slightest of punctate lesions outside the dendritic area were included. Other workers have described a much lower rate of punctate keratopathy in patients on ACV treatment, namely, 14%[15] or none in 30 patients.[13] After discontinuation of the treatment the punctate keratopathy disappeared in an average of

8·5 days in the ACV series and 7·6 days in the TFT series. Surprisingly, the ACV-treated group had the same frequency of punctate keratopathy as the TFT-treated group. If this effect is caused by a metabolic disturbance of the corneal epithelium due to DNA inhibition, we should expect less keratopathy in the ACV group, as ACV is known not to inhibit cell DNA polymerase. Moreover, Lass *et al.*[16] found that ACV had no detrimental effect on regeneration of corneal epithelium. However, we do not know to what extent the keratopathy may be related to the ointment base used.

Our results indicate that both ACV and TFT are safe, have a high therapeutic efficacy against dendritic herpetic keratitis, and are of low toxicity.

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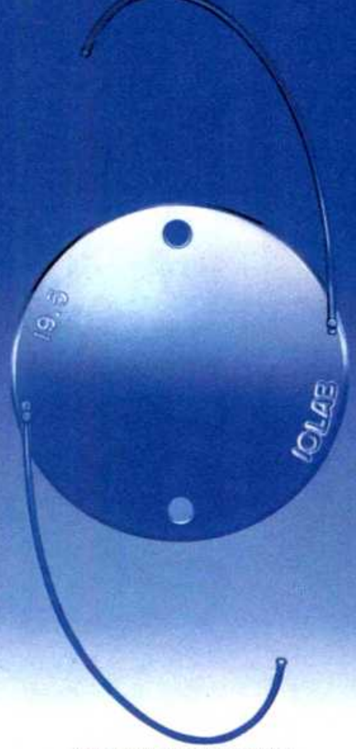

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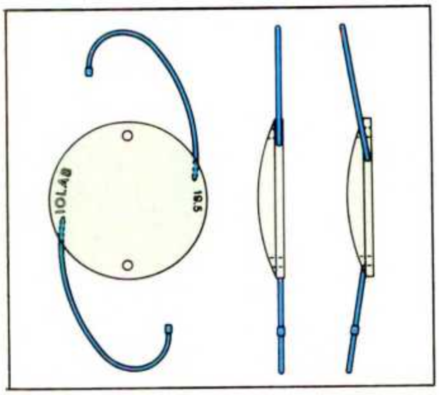

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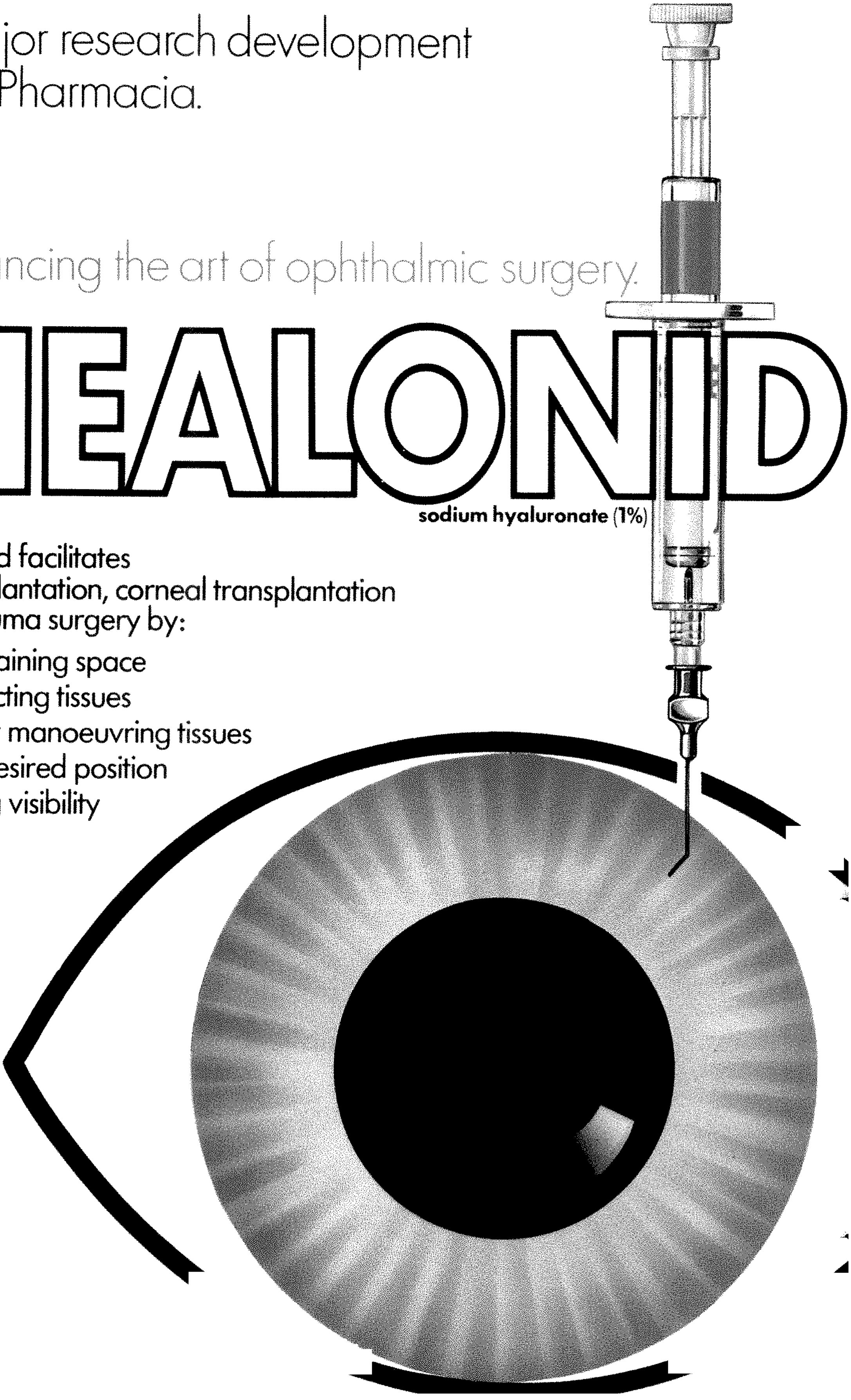

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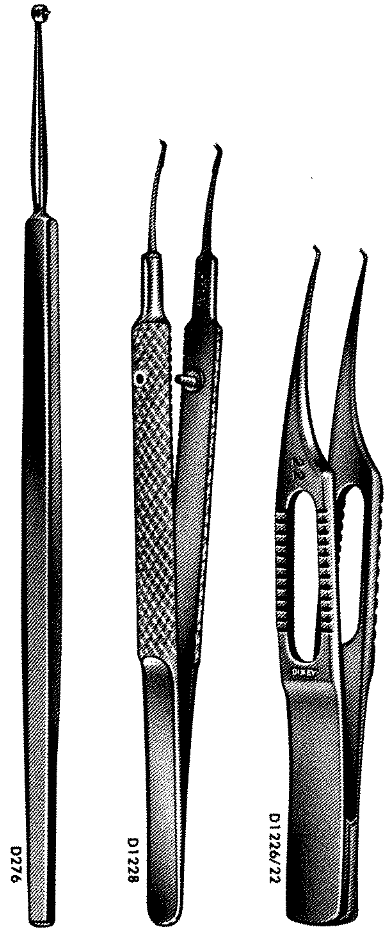

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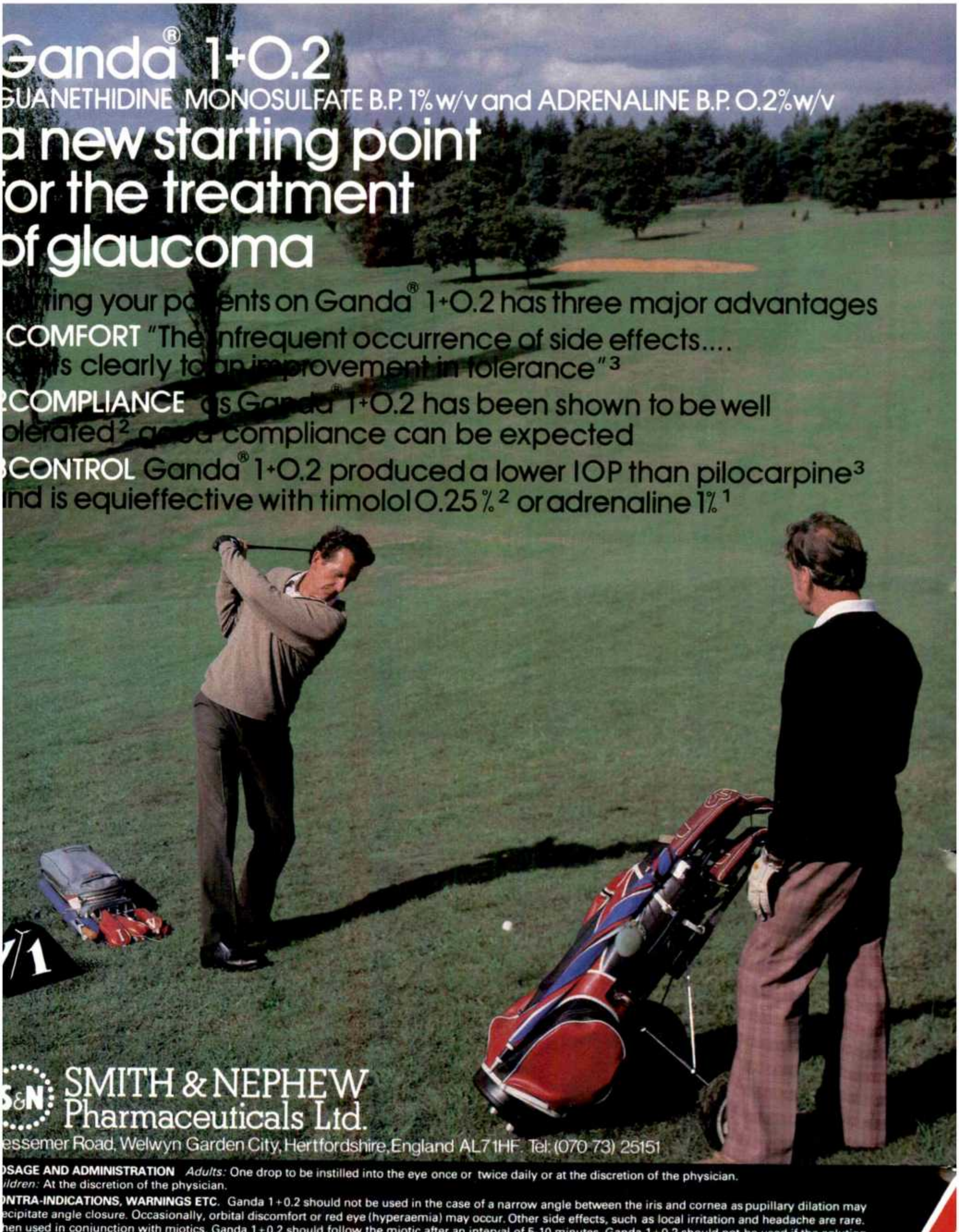

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Combination therapy for dendritic keratitis with human leucocyte interferon and trifluorothymidine

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SUMMARY Sixty-one patients were treated in a randomised double-masked clinical trial either with a combination of human leucocyte interferon 10 million IU/ml and trifluorothymidine (TFT) in a 1% solution or with a combination of albumin placebo and trifluorothymidine. The healing time of dendritic keratitis was significantly lower with the combination of interferon and TFT than with the combination of placebo and TFT. For partial healing the reduction was 49% and for complete healing 42%.

Herpes keratitis is still considered to be one of the most serious diseases of the outer eye. With the advent of virostatics[1] in 1962 there has been progressive improvement in the treatment of dendritic keratitis. At present interferon treatment is at the centre of interest. It was discovered in 1957, but as it was very difficult to produce in large quantities experiments[2 3] were limited.

Studies with interferon or interferon inducers alone[4–9] in controlling dendritic keratitis gave disappointing results. In combination with virostatics[4 10] interferon was reported to be more effective than virostatics alone.

We have treated patients with dendritic keratitis and superficial epithelial lesions with interferon or placebo in combination with trifluorothymidine in a double-masked randomised trial.

Material and methods

Patients with dendritic keratitis or morphological variants were treated in a randomised arrangement with eye drops containing either human leucocyte interferon (HLI) 10 million IU/ml and trifluorothymidine (TFT) in a 1% solution, or albumin placebo and trifluorothymidine in a 1% solution.

Patients with metaherpes,[11] stromal keratitis, or who had previously received steroid treatment were excluded from the trial.

All patients received 5 drops of TFT daily. In addition they received every morning after careful eye examination one drop of HLI[12] or placebo in a recumbent position. After 10 minutes a second drop was given, and the patients remained recumbent for another 10 minutes to ensure that the HLI or placebo kept in contact with the surface of the outer eye.

Before treatment we isolated herpes simplex virus from the cornea and conjunctiva by minimal wiping. Virus identification was done at the National Institute of Public Health in Bilthoven, The Netherlands. During transport and storage eye swabs were kept in GLY-medium, i.e., Hanks's balanced salt solution containing 0·5% gelatin, 0·5% lactalbumin hydrolysate, 0·1% yeast extract, and antibiotics. The specimens were inoculated onto HEp-2 and on to GaBi cells (human diploid fibroblasts) in tubes. Cultures with characteristic cytopathic effect were identified as herpes simplex virus by serum neutralisation in GaBi cells. Typing was done in GaBi cells in microplate culture, with the use of rabbit antisera monospecific for type 1 and type 2, respectively.

We used 2 criteria for healing: (1) partial healing, which we defined as closure of the epithelial wound only, i.e., no staining with fluorescein; and (2) complete healing, which we defined as closure of the epithelial wound without any epithelial oedema or cystic changes in the area of the previous dendrite.[13] We gave the HLI or placebo until the third day of partial healing; the TFT was continued till complete healing.

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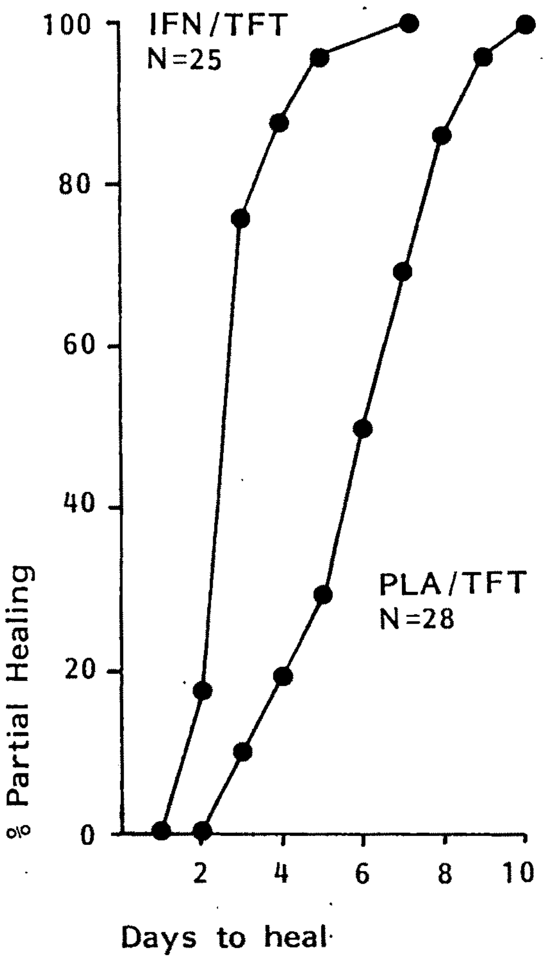

Fig. 1 *Cumulative frequency graph for partial healing time of dendritic keratitis treated with interferon/TFT or placebo/TFT.*

Results

Eight patients were excluded from the study, 2 because of omissions in complying with the examination protocol, one because he developed metaherpes; this patient received the placebo/TFT combination. Three patients were excluded because all herpes simplex virus isolations were negative. Two other patients developed severe stromal keratitis; both received the placebo/TFT combination.

Of the remaining 53 patients (33 males and 20 females) 25 were treated with HLI and TFT (15 males and 10 females) and 28 were treated with placebo and TFT (18 males and 10 females).

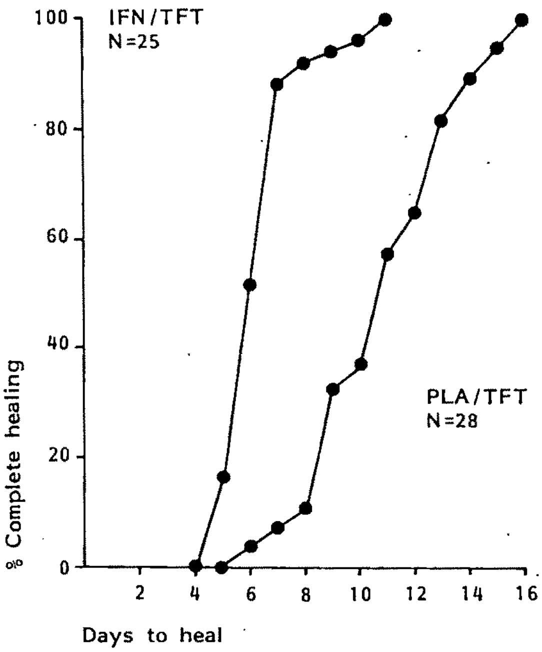

Fig. 2 *Cumulative frequency graph for complete healing time of dendritic keratitis treated with interferon/TFT or placebo/TFT.*

In Fig. 1 the number of days for partial healing of dendritic keratitis is given in a cumulative frequency graph. The average time for partial healing of the interferon/TFT treated group was 3·3 days and of the placebo/TFT treated group 6·5 days.

Table 1 is the table of analysis of variance for the data of partial healing. The treatment effect was statistically highly significant (p<0·01).

In Fig. 2 the number of days for complete healing of dendritic keratitis is given in a cumulative frequency graph. The average time for complete healing of the interferon/TFT treated group was 6·6 days and of the placebo/TFT treated group 11·3 days. The treatment effect of complete healing was also statistically highly significant (p<0·01).

Table 1 *Analysis of variance of partial healing time*

Nature of effect	*Source*	*Sum of squares*	*DF*	*Mean sum of squares*
Main factors	Therapy (T)*	136·94	1	136·94
	Sex (S)	2·32	1	2·32
	Eye (E)	0·93	1	0·93
Interactions	T×S	2·37	1	2·37
	T×E	3·53	1	3·53
	S×E	1·20	1	1·20
Residual		111·68	46	2·43
Total		258·97	52	

DF=degrees of freedom. *p<0·01.

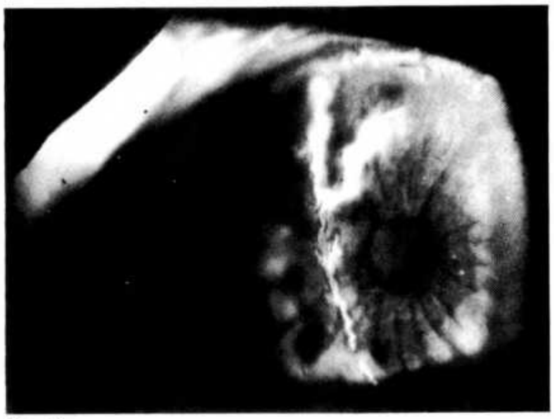

Fig. 3a

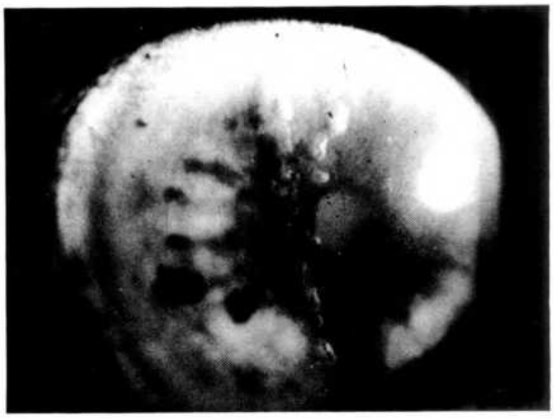

Fig. 3b

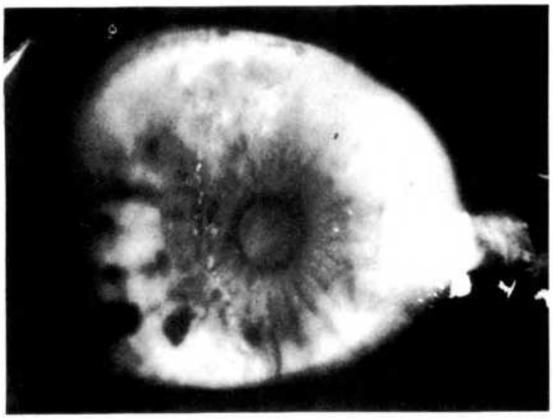

Fig. 3c

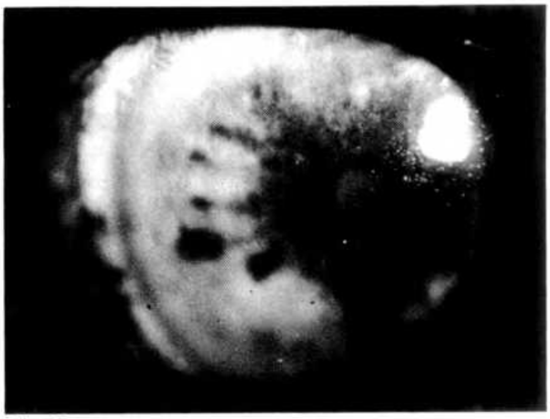

Fig. 3d

Fig. 3 *These photographs show the healing process of dendritic keratitis after treatment with the interferon/TFT. (a) Before treatment. (b) One day after treatment. (c) Two days after treatment. (d) Three days after treatment.*

The interval in days between partial and complete healing of dendritic keratitis for the interferon/TFT treated group was 3·3 days and for the placebo/TFT treated group 4·8 days. This difference was statistically significant ($p<0·01$).

The healing process after treatment with interferon/TFT is illustrated in Fig. 3, a–d.

Discussion

Only those corneal herpetic lesions were studied in this trial in which active virus replication was present in the epithelial cells. We therefore excluded metaherpes, which is considered to be a trophic herpetic disease, and also stromal forms in which immunological reactions rather than virus replication are the important factor.

Many authors[4–9] have concluded that interferon or interferon inducers alone did not significantly reduce the healing time of dendritic keratitis as compared with the natural healing time.

Our results indicate that the combination of interferon and TFT gave a lower healing time for dendritic keratitis than TFT alone. In addition the 2 forms of treatment led to a quicker healing time than leaving the ulcers untreated. We have previously recorded a natural partial healing time of 13·8 days (SD=4·1) and a natural complete healing time of 20 days (SD=3·6).[14] In the present trial for TFT alone the comparable data are 6·5 days (SD=1·5) and 11·3 days (SD=2·6) respectively. The percentage gain for TFT alone is 53% for partial healing and 44% for complete healing. If interferon is used in combination with TFT, these data are 3·3 days (SD=1·1) and 6·6 days (SD=1·4) respectively. Here the percentage gain as compared with the natural healing time is 76% for partial healing time and 67% for complete healing time.

Because there is a difference in the interval between partial and complete healing of the interferon/TFT treated group and the placebo/TFT treated group, we may assume that the virus still exists in the period between partial and complete healing.

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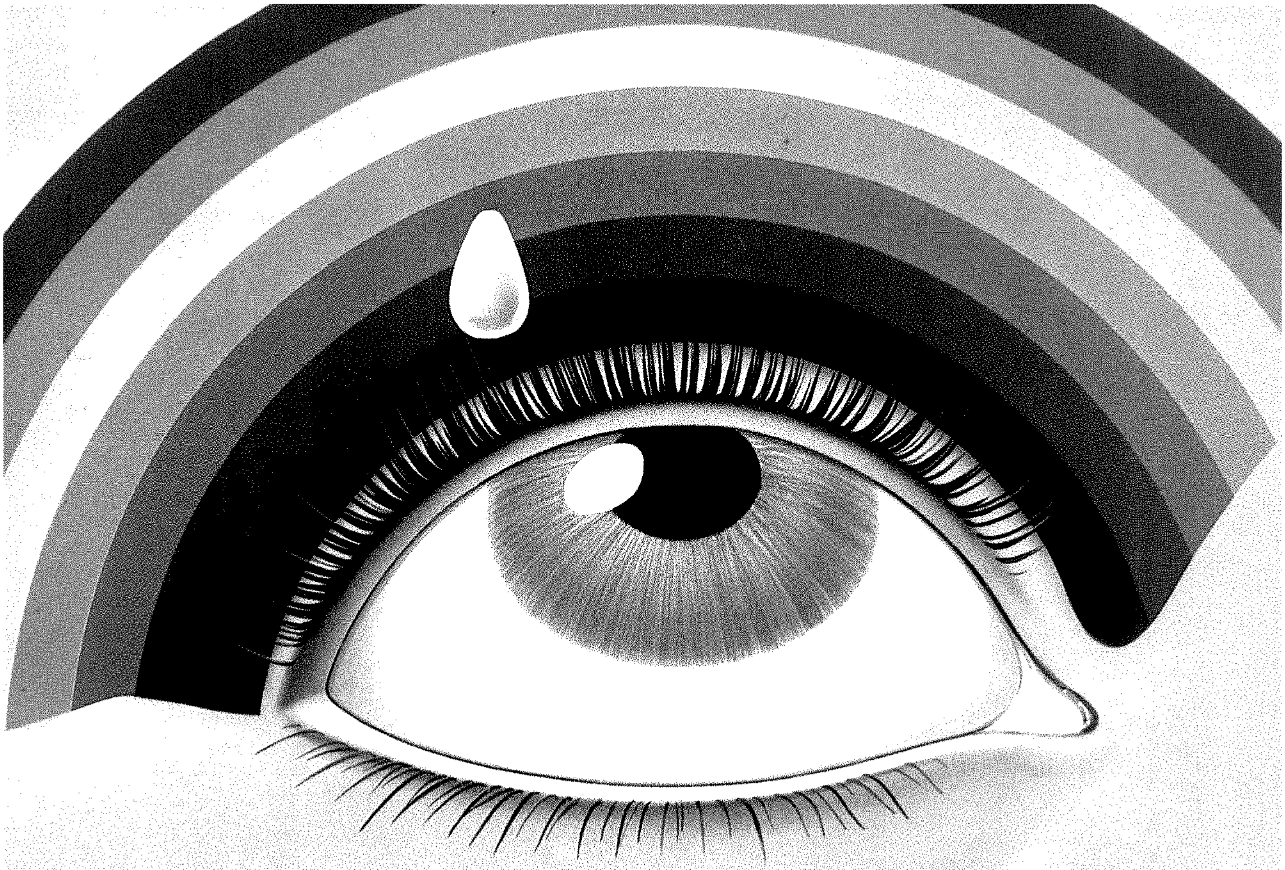

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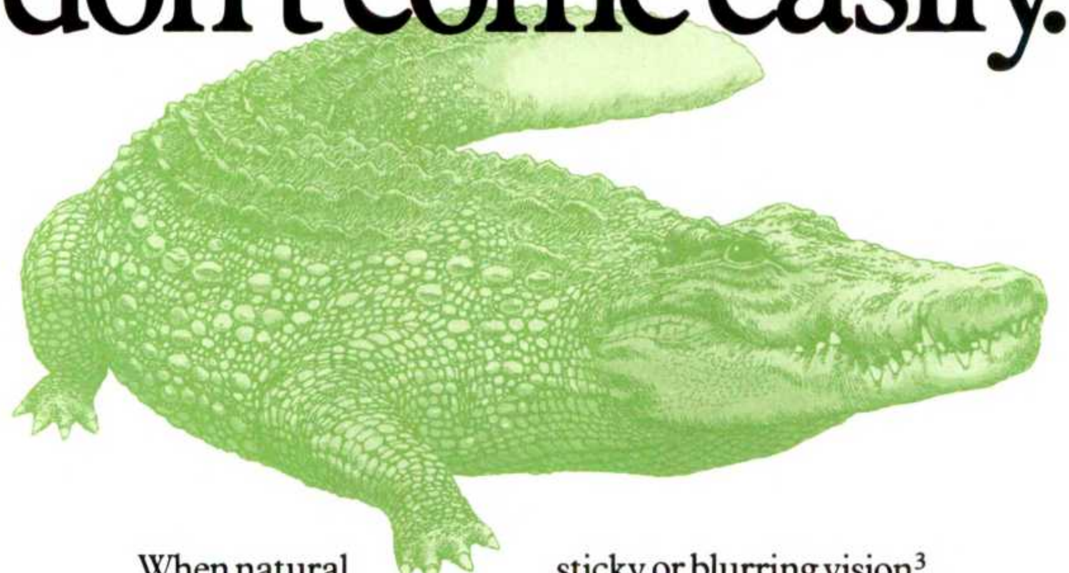

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British Journal of Ophthalmology, 1982, **66**, 513–515

Effect of age on the endothelial cell count in the normal eye

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SUMMARY The endothelial cell count was studied in 275 normal eyes. It showed a gradual decline to the age of 50 but no appreciable difference thereafter. Review of earlier reports of progressive reduction throughout life indicates that a different interpretation is likely, which conforms with the results of this and other recent studies. The value of detailed endothelial studies is discussed briefly.

Corneal clarity is maintained by the endothelial layer possessing the ability to pump water out of the corneal stroma against an osmotic gradient. To perform this function the endothelial layer must consist of healthy cells above a minimum cell density. If the average cell count per square millimetre falls below 1000, it is likely that stromal oedema and bullous keratopathy will ensue. This paper reports the effects of age on the endothelial cell density.

Subjects and methods

Two hundred and seventy-five eyes were photographed which showed no evidence of clinical disease and had not suffered any insult to the anterior segment in the form of accidental or surgical trauma. The patients were drawn from 2 main groups. The smaller and younger age groups were those patients who had had corneal injuries to the fellow eye, with no evidence of pathology in the eye studied; the second and larger group was of patients who were admitted to hospital for cataract extraction or who had had cataract surgery to the fellow eye. The proportion of patients in age groups is as shown (Fig. 1).

Endothelial counts were performed by taking 3 or more photographs with the Heyer-Schulte specular photomicroscope and performing fixed-frame counts from black-and-white enlargements.

Results

The scatter of cell counts with age is shown in Fig. 2, which gives an average cell count for the whole group of 3227 cells/mm^2 with a standard deviation of 554. The mean cell count for each decade shows a gradual decline up to the age of 50. In the succeeding decades there is no appreciable difference between the age groups, with the mean cell counts for each age group lying within 60 cells/mm^2 of 3200 cells/mm^2 (Fig. 3).

Discussion

Irvine and Irvine[1] reporting on histological preparations of normal eyes taken from subjects aged between 25 and 84 showed no evidence of variation with age. The first reports on the use of specular microscopy by Laing[2] and Bourne and Kaufman[3] showed a reduction of in-vivo cell count with age, and

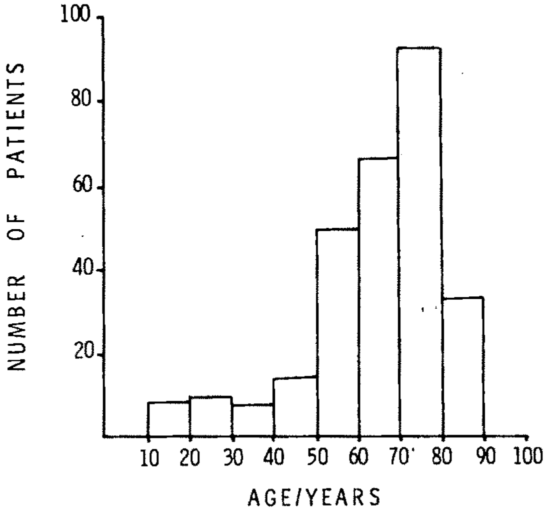

Fig. 1 *Ages of patients grouped in decades.*

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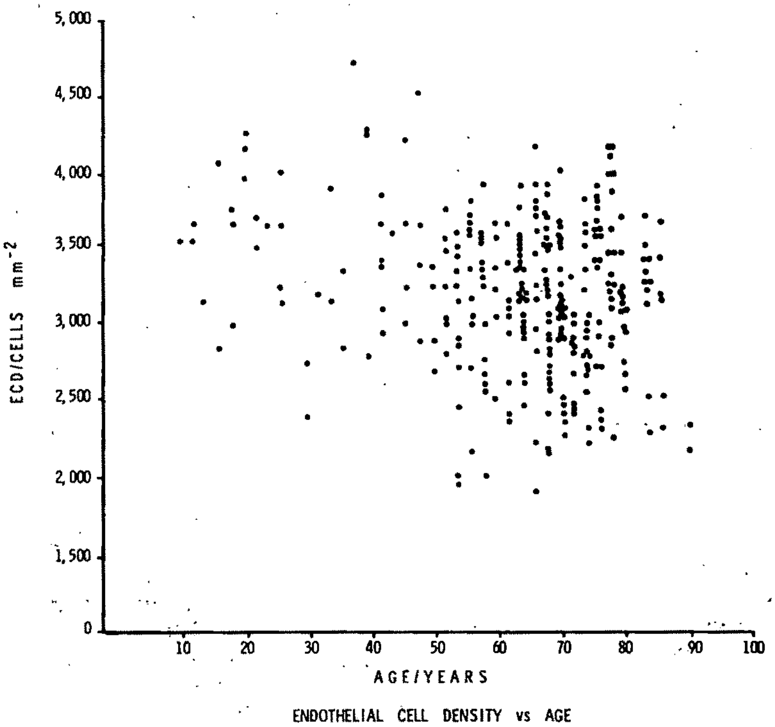

Fig. 2 *Scatter of cell counts by age.*

a later study by Laule *et al.*[4] demonstrated a steep decline in cell count with age up to the age of 25, followed by a more gradual decline in subsequent years. This result extrapolated to a cell count of zero at the age of 100 years.

More recent studies, including our own, show a less significant decrease in cell count in the older age groups. Sturrock *et al.*[5] reporting on a series of 97 eyes describe an age related decrease in cell count over the entire age group, but on review of their data there appears to be a higher count in the younger age group, up to the age of 25, followed by a nearly static average cell count in the subsequent years. Price and Barbour[6] also present a series in which they describe a reduction of endothelial cell density with age. Their graph, however, shows a reduction until the fifth decade but no subsequent fall in the mean endothelial count beyond this age. Hiles *et al.*[7] studied a group of 266 eyes in patients between the ages of 8 months and 24 years and found a drop of 500 cells/mm² in the first 4 years, followed by a static phase from 5 to 20 years. Our results suggest a drop in mean population cell count up to the age of 50, which is rather later than shown in other reports. Hoffer and Kraff[8] in an extensive study of 1523 patients between the ages of 40 and 90 show no significant drop in cell count at all.

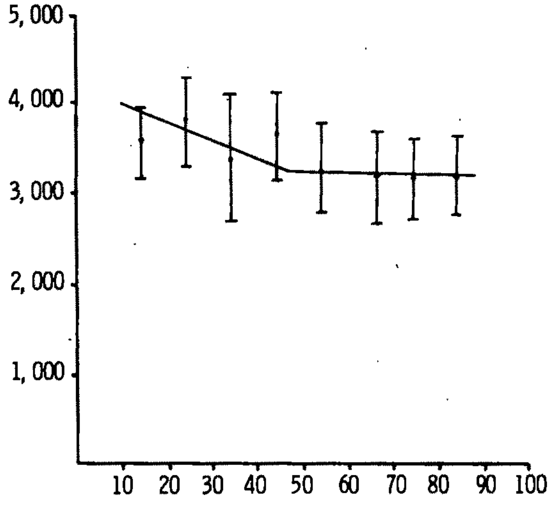

Fig. 3 *Mean cell counts for each age group.*

It therefore appears that there is a reduction in cell count during early adulthood, followed by a stabilisation of the cell count throughout the remainder of life.

The metabolically very active cells have to function without replacement for many years, retaining the ability to repair defects by expansion and migration. In the course of anterior-segment surgery a proportion of cells is lost. If the endothelial cell count has already become reduced to a critical level, there is a risk that cells lost owing to surgical trauma will precipitate an endothelial decompensation.

Since it is not possible to assess the cell count by reference to age, it is necessary to perform specular microscopy to ascertain the cell density. There is a large population variability, but in the clinically healthy cornea it is so unusual to find a pathologically low cell count that it is questionable whether detailed specular cell studies have any place prior to routine surgical procedures. There remains the necessity for cell density estimations for research, in the study of the prevention of surgical trauma, and in the clinical management of the pathological cornea. If multiple surgery is planned, specular microscopy should be performed prior to subsequent stages. The greatest need for these studies is in the assessment of differences in cell loss during operations, either due to changes in technique or to the potential toxicity of materials introduced into the anterior chamber.

Contrary to earlier reports, recent studies show no significant endothelial cell loss beyond middle age. Detailed specular microscopy with cell counts and morphological study is unnecessary as a routine, although its value in research studies remains considerable.

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British Journal of Ophthalmology, 1982, **66**, 516–517

Reduction in endothelial cell density following cataract extraction and intraocular lens implantation

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SUMMARY Comparison of endothelial cell density by specular photomicroscopy of the right and left eyes after single eye surgery shows a similar reduction in endothelial cell density to that recorded between pre- and postoperative photographs in the operated eye. A review of 43 single-eye cataract extractions, with and without placement of a prepupillary intraocular lens, confirms that the major cause of endothelial cell loss is operative trauma to the endothelium. In our experience a cataract extraction with lens implantation but without endothelial contact produces no greater reduction in cell density than the cataract extraction alone.

Since the modification of specular microscopy for clinical use by Laing *et al.*[1] and Bourne *et al.*[2] many reports have been published on the reduction in endothelial cell (EC) density following surgery involving the anterior chamber. This research has mainly been carried out by comparing the EC density pre- and postoperatively in the operated eye. Sugar *et al.*[3] reported on 83 patients who showed a reduction in EC density in the operated eye as compared with the unoperated fellow eye, but question the accuracy of this technique. We have compared the results from a group of patients studied by both methods.

Secondly, we report on a small group of patients studied by the retrospective method of comparing operated with unoperated eyes following intracapsular cataract extraction with and without the incorporation of an intraocular lens.

Patients and methods

Fifteen patients had pre- and postoperative specular photomicroscopy of both eyes, and again at an interval of greater than 3 months (average 9·3 months) following single-eye surgery. Forty-three patients were studied who had undergone single-eye cataract surgery, 33 with and 10 without the incorporation of an intraocular lens. We calculated the difference in EC density between the operated and unoperated fellow eyes at an average of 16·7 months after surgery.

Three photographs were taken of each eye with the Heyer-Schulte corneal endothelial camera (Model HS CEM3), and the EC density was averaged for each eye from black-and-white enlargements.

The plan of surgery was identical in every case and performed by one surgeon (M.J.R.H). All patients were given general anaesthesia. A 2-plane 170° corneal incision was used. Two peripheral iridotomies were made, and all cases received alpha-chymotrypsin prior to intracapsular cryoextraction of the lens. Acetylcholine (Miochol) and air were used to reform the anterior chamber during closure.

In those cases with intraocular lens this was a wet-pack Binkhorst 4-loop lens (Rayner), placed obliquely, with a single iris stitch around the upper anterior loop. The wound was closed with a single preplaced 8/0 (0·4 metric) virgin silk and a continuous 10/0 (0·2 metric) polyamide suture. During closure air was used to maintain the anterior chamber. The air was then removed and replaced with balanced salt or acetylcholine solution. Watertight closure was confirmed.

During the procedure any endothelial contact with the intraocular lens was recorded and coded as nil, brief contact with no rubbing, or prolonged contact, with or without a rubbing force being applied.

Results

The 15 patients who were photographed pre- and post-operatively showed a mean reduction of EC density of 16·9% (SD 4·6). The comparison between

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the right and left eyes of this group of patients showed a reduction of 16·5% (SD 4·5). There is no significant difference between these results.

The 43 patients who were studied retrospectively were divided into the 4 groups and showed the reduction in EC density in the operated eye as set out in Table 1. This gives an overall reduction in EC density of 23·2% in the 33 patients with intraocular lenses.

Table 1 *Results of operation*

	Endothelial trauma	*Number of patients*	*Mean EC density decrease*	*SD*
Cataract extraction	0	10	13·1	6·2
Cataract extraction with IOL	0	18	11·7	12
	Brief	11	26·1	11·7
	Prolonged	4	52·3	8·5

Discussion

The similarity between results when comparing pre- and post-operative EC densities shows that the retrospective study of single-eye surgery and its effects on the endothelium is feasible. Retrospective studies should not be used in preference to prospective work, but this technique is the only method possible in the study of cases where pre-operative EC density measurements are not possible, for example, in the study of the effects of accidental corneal trauma.[4,5]

Our series of patients who underwent cataract extraction with intraocular lens gives a very similar result (23·2% drop in EC density overall) to the prospective studies as reviewed by Bourne *et al.*,[6] which gave an overall reduction of EC density of 23·8% in 542 cases. The reduction of EC density related to endothelial trauma is comparable with the retrospective results of Sugar *et al.*[3]

Those cases in which there was no evidence at operation of endothelial damage during the intraocular lens insertion show a similar reduction of EC density to the cases where cataract extraction was performed without the intraocular lens. In the presence of endothelial contact with the implant for a short period, and where no rubbing force was applied, the reduction of EC density is greater, but still remains within levels compatible with long-term retention of endothelial function. It is with prolonged endothelial contact, and particularly where the lens is rubbed against the endothelium, that an unacceptably large reduction of EC density occurs.

It is apparent that the final decision as to the placement of the intraocular lens must be taken at surgery. If the anterior chamber will not deepen sufficiently for the surgeon to insert the lens without prolonged endothelial contact or rub, then the high levels of reduction of EC density, which can be expected, indicate that lens insertion should not proceed. This decision is especially difficult to make in a situation where an intraocular lens is most desirable, for example, in the presence of a high preoperative hypermetropic refractive error, or if the fellow eye is already functioning satisfactorily with an intraocular lens in situ. Protective agents such as sodium hyaluronate show promise in preventing endothelial cell loss in this situation.[7]

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British Journal of Ophthalmology, 1982, **66**, 518–519

Changes in endothelial cell density following accidental trauma

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SUMMARY Specular photomicroscopy on 25 patients who had accidental perforating injuries affecting the anterior segment of the eye revealed the major cause of cell loss to be the intraocular manipulation of foreign bodies and secondary surgery.

Subjects and methods

Twenty-five patients were studied, who had attended the Birmingham and Midland Eye Hospital or associated hospital units. They ranged in age from 12 to 77 (mean 32·2) years and the corneal endothelium was studied from 3 months to 15·5 years (mean 25·7 months).

Both eyes of each patient were photographed, 3 or more exposures being taken of each eye, with the Heyer-Schulte specular microscope; fixed-frame counts were made from black-and-white enlargements. The percentage cell density change was recorded as a direct comparison between the traumatised and normal eyes, none of which showed any sympathetic inflammation.

Results

All the patients had perforating injuries affecting the anterior segment of the eye. Eight patients had injuries from shattered windscreens; 5 patients were hit by thrown objects; 4 sustained lacerations from sharp metal objects; 4 were hit by metal when hammering, including 3 with posterior segment intraocular foreign bodies. Two had lacerations from broken spectacles, one suffered a perforation from hot metal and one walked into a ladder.

Of the 3 patients who had posterior segment foreign bodies 2 had the foreign body removed as a late procedure, which involved no anterior segment surgery. All other patients underwent emergency corneal repair within 24 hours.

The average drop in cell count was 14·75% (SD 19·08), of which 14 patients (56%) had a drop of less than 10%. Out of 18 patients in whom the depth of the anterior chamber was noted at presentation to the hospital 3 were recorded as having flat anterior chambers. They showed a cell loss of 12·36%, which is not significantly different from those 15 with formed anterior chambers (13·6%).

Seven patients had lens surgery. One had lens aspiration at the first procedure with a cell loss of 3·5%. Three had lens aspiration/irrigation as a late procedure and had an average cell loss of 22·9%. One patient underwent a lensectomy/vitrectomy, which was complicated by a wound leak requiring a secondary repair, and had a cell loss of 41·6%. One patient required a late needling following a lens aspiration at the original repair and had a cell loss of 72·5%. One patient had a corneal and lens perforation from a piece of metal which was subsequently removed through a sclerotomy without any anterior segment repair. Two years later he underwent an intracapsular cataract extraction with insertion of a Binkhorst 4-loop intraocular lens, during which there was no contact with the endothelium. He was recorded 10 months later as having a cell loss of 34·3%.

The average cell loss of those cases without secondary lens surgery was 7·9% ($n=19$) and those cases with secondary surgery was 36·19% ($n=6$), which is highly significant ($p<0·01$).

Three cases had foreign material in the anterior chamber. Two had glass and one had glass and lashes. The average cell loss for these 3 was 21·7%.

Apart from the 3 cases above and those cases which had secondary lens surgery 9 cases had lacerations extending less than half the corneal diameter, with an average cell loss of 3·7%, and 5 had lacerations

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Table 1 *Results*

		Number	*% drop*	*Significance*
Anterior chamber depth	Flat	3	12·35	Nil
	Formed	15	13·6	
Secondary lens surgery	Yes	6	36·19	p<0·01
	No	19	7·98	
Extent of laceration	<Half	5	5·33	Nil
	>Half	9	3·7	

extending for more than half the corneal diameter, with an average cell loss of 5·33%. The difference between these 2 groups is not significant (Table 1).

Discussion

Comparison of operated with unoperated eyes for estimation of changes in endothelial cell densities has been shown to correlate closely with pre- and postoperative counts in unilateral cataract surgery.[1] It has been necessary to assume a similar correlation holds for accidental trauma, where no earlier cell counts were available. No cases were studied earlier than 3 months after the final procedure, as this has been found to be the period after which little alteration in cell density occurs.[2]

Studies of surgical trauma in planned cataract surgery and intraocular lens implantation reveal that direct endothelial damage is the major cause of cell loss.[3,4] To a lesser degree cells are lost by the cytotoxic nature of various substances on the endothelium, which may be introduced into the anterior chamber.[5,6]

Slingsby and Forstot[7] have shown that blunt corneal trauma, without any entry into the anterior chamber, can have a significant effect on endothelial cell density, although this difference is small, 6·4% loss in a series of 25 patients. The cell loss, which we have found in a similar number of patients with penetrating injuries, was smaller than would be expected, as each patient, in addition to a significant contusion to the globe, would have received a variable amount of intraocular manipulation. It was only when extensive endothelial trauma occurred, either from traumatically implanted foreign bodies or when secondary surgery was performed, that large drops in cell density were found.

There are points to be clarified by a more extensive prospective study. We have found a wide range of results, over which the average has been taken. Larger numbers of subjects may have an effect on the overall result. More detailed monitoring should be made of the instrumentation and fluids used within the anterior chamber during the primary and secondary surgical procedures.

The cases which have had secondary procedures have widely differing changes in cell density, and it may be that the endothelium, which is in the process of migrating to cover bare areas, has an increased susceptibility to further trauma during the secondary procedure. Although the original cell loss is small in uncomplicated perforating injuries, a secondary procedure—for example, a secondary combined lens aspiration with intraocular lens insertion—may result in considerably greater cell loss than would be expected were this to be carried out as a primary procedure on a previously untraumatised eye.

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British Journal of Ophthalmology, 1982, **66**, 520–523

Corneal evaluation of prospective aphakic wearers of contact lenses

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SUMMARY The corneal response of a group of the affected eyes of prospective monocular aphakic wearers of contact lenses as compared with that of their normal fellow eyes was studied. The results show a reduced corneal sensitivity and endothelial cell density but identical centre corneal thickness and corneal oxygen uptake.

A recent investigation[1] has shown that the cornea of the aphakic eye swells less than that of the normal fellow eye when fitted with identical hydrophilic lenses. This confirms previous clinical impressions and would suggest that a metabolic difference may exist between the corneas of the normal and the aphakic eye.

The present investigation was therefore devised to assess certain aspects of the basal corneal metabolism of a group of monocular aphakic patients, the fellow normal eye being used as the control.

Material and methods

Corneal physiology was investigated by means of 4 highly sensitive methods. (1) *Aesthesiometry.* The touch threshold of the central cornea (CTT), which is the inverse of sensitivity, was measured by the Cochet-Bonnet aesthesiometer. (2) *Pachometry.* A digital pachometer attachment to the slit lamp was used to measure the central corneal thickness. (3) *Corneal oxygen uptake.* A polarographic method was chosen to measure the corneal oxygen needs. (4) *Endothelial photography.* The corneal endothelial density was calculated from photographs taken with the Holden-Zantos attachment to the slit-lamp. For each method the usual precautions regarding measurements and calibration have been taken as described in previous publications.[2 3]

The patients chosen were all monocular aphakes who had been considered suitable for contact lens wear (Table 1). The criteria for selection were: (1) no problems at surgery; (2) good general health; (3) no ocular abnormality of the nonaphakic eye (apart from occasional lenticular opacities); (4) no previous surgery on the nonaphakic eye which was used as a control.

To avoid any diurnal variation all the tests were carried out at the same time of the day, and each patient had been awake for more than 2 hours.[4]

Results

The 4 basic measurements were attempted on all 20 patients. Because of difficulties with patient co-operation endothelial photography and corneal sensitivity determination were possible in only 18 cases and oxygen uptake measurement in 16 cases. Pachometry results were obtained for all 20 patients.

For each technique the intrinsic values and percentage difference between the aphakic and phakic eyes were recorded:

$$\%\ \text{Difference} = \frac{A-P}{P} \times 100\%.$$

CORNEAL SENSITIVITY

The central corneal touch threshold (CTT) for the aphakic eyes was significantly higher than for their fellow phakic eyes, 44·0±50·5 mg/mm^2 (range 12 to 200·0 mg/mm^2) vs. 15·8+7·2 mg/mm^2 (range 12 to 36 mg/mm^2). Further the aphakic eyes showed a much larger CTT scatter than the control group, suggesting

Table 1 *Summary details of patients*

Age	*Time since surgery*	*Type of surgery*	*Aphakic eyes*
59·6±12·0 yr	55±82 weeks	Intracapsular 14	11 Right
39–81 yr	6–320 weeks	Extracapsular 5	9 Left
		Aspiration 1	

Correspondence to Dr M. Guillon.

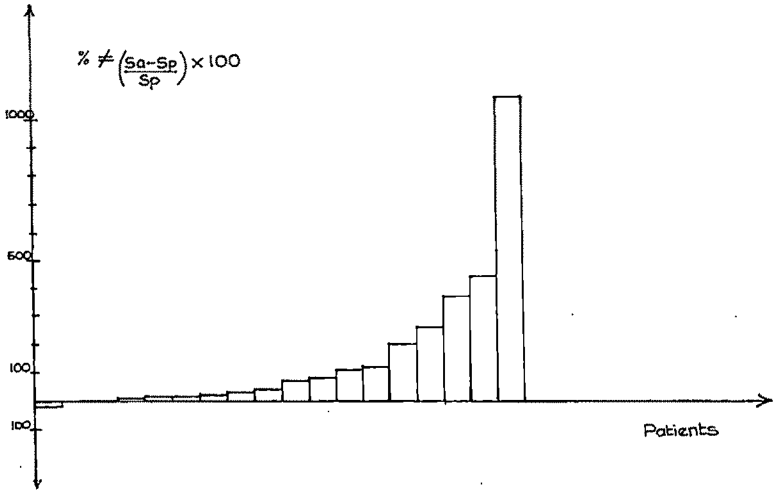


Fig. 1 *Histogram showing the percentage difference in CTT between aphakic and phakic eye for each patient.*

that the effect of surgical procedure on the corneal sensitivity varied widely. Even when the same surgical procedure was considered (here intracapsular extraction, which was encountered in the largest number of cases), a large variation in results was encountered, 51·0±54·5 mg/mm^2 (range 13·0 to 200·0 mg/mm^2).

The percentage difference for each patient between the aphakic and control eye was +152·9%± 261·2% (range −23·9% to +1085%) and showed that with one exception the aphakic eye was less sensitive than the control eye (Fig. 1).

Because of the large individual variations nonparametric statistics were used (sign test). They showed that the difference was significant at the 1% level.

CENTRAL CORNEAL THICKNESS

The mean central corneal thickness for the aphakic eye only was marginally higher than for the control group (0·522±0·032 mm (range 0·477 to 0·584 mm) vs. 0·518±0·022 mm (range 0·462 to 0·561 mm). The values obtained being regularly distributed a non-independent t test was carried out and showed no significant differences between the 2 groups (t=0·626).

The percentage differences for each patient were normally distributed (Fig. 2) between −9·8% (thicker control eye) and +7·7% (thicker aphakic eye), with a mean value +0·72%±3·74%.

CORNEAL OXYGEN UPTAKE

The mean corneal oxygen uptake of both groups was identical: 2·77±0·39 μl O_2 (STP/cm^2 h) (a range 1·89

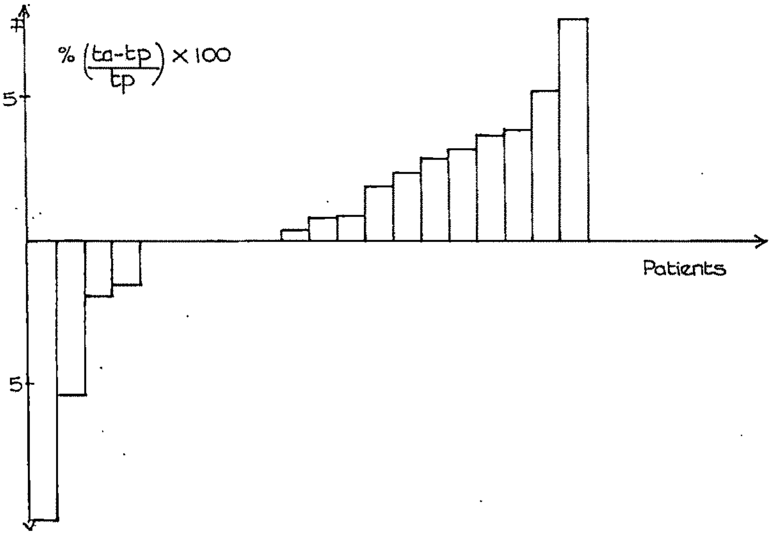


Fig. 2 *Histogram showing the percentage difference between the central corneal thickness of aphakic and phakic eye for each patient.*

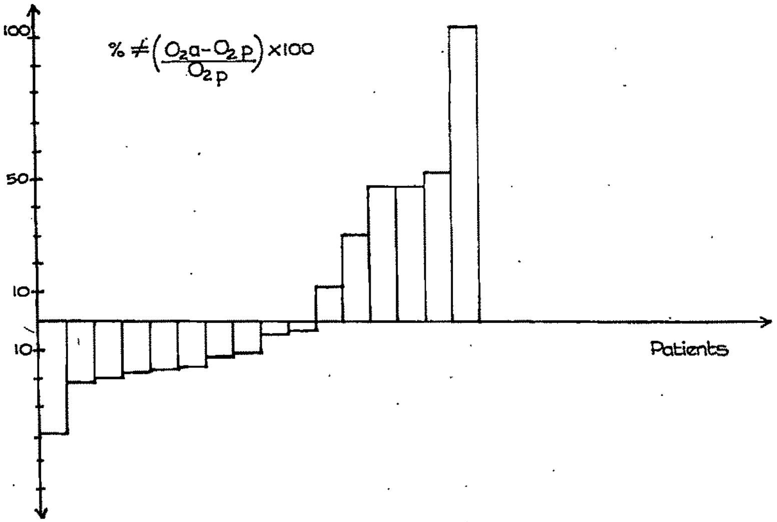


Fig. 3 *Histogram showing the percentage difference in corneal oxygen uptake between aphakic and phakic eye for each patient.*

to 3·35 μl O_2 (STP/cm^2 h) for the aphakic eyes and 2·77±0·74 μl O_2 (STP/cm h (range 1·37 to 3·98 μl O_2 (STP)/cm^2 h) for the phakic eyes.

The percentage difference was randomly distibuted from −41·3% to +104·4% (Fig. 3), with a mean of +8·11±38·3%, which is not statistically significant.

ENDOTHELIAL CELL DENSITY

The mean endothelial cell density for the aphakic eyes was lower than for the phakic eyes: 2867±442 cells/mm^2 vs. 3189±432 cells/mm^2. Because of the large individual variations nonparametric statistics were used, the sign test being significant at the 1% level.

The % difference for each patient was −9·66%± 15·9%, (range=+5·6% to −5·5%), with a predominantly lower density for the aphakic eye (Fig. 4).

Discussion

As expected, the corneal sensitivity of the aphakic eye is lower than for the fellow nonoperated eye. Millodot[5] and Millodot and O'Leary[6] have shown a correlation between decreased corneal sensitivity and corneal oedema for normal patients. For our group of aphakic corneas the loss of sensitivity cannot be explained in terms of basal metabolic differences. When the CTT is plotted against the corneal oxygen uptake (an indication of the epithelial metabolism) (r=−0·28) and against corneal thickness (an indicator of the stromal metabolism) (r=−0·33) no correlation is detectable.

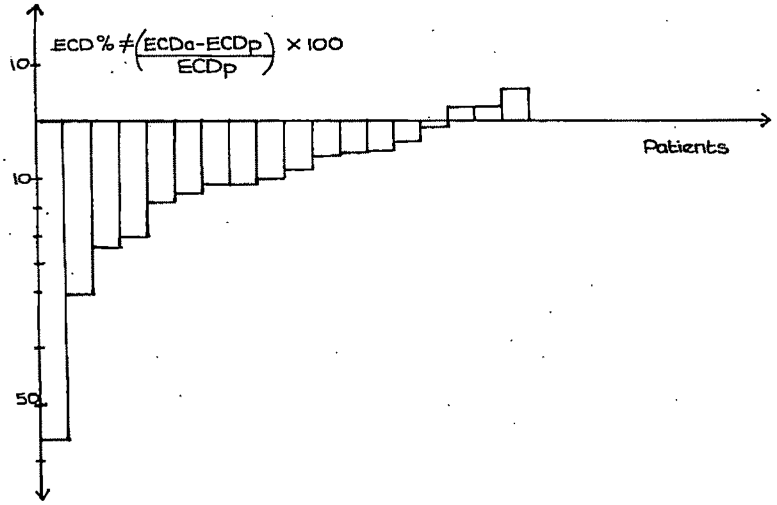
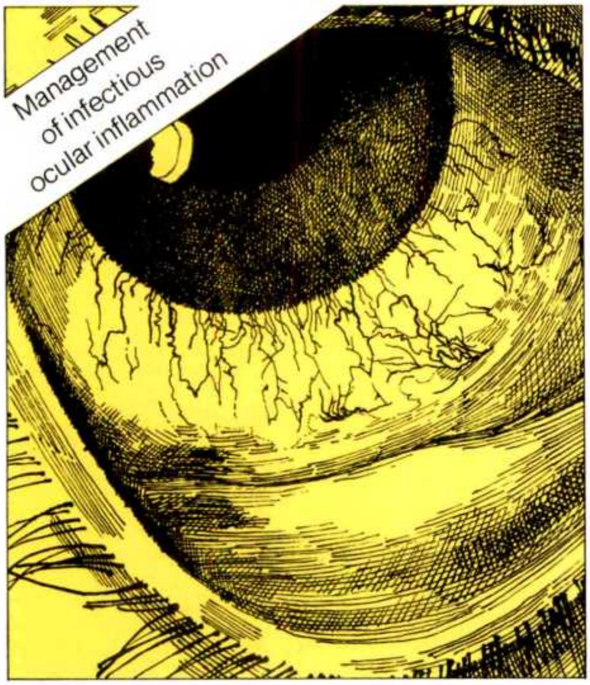


Fig. 4 *Histogram showing the percentage difference in endothelial cell density between aphakic and phakic eye for each patient.*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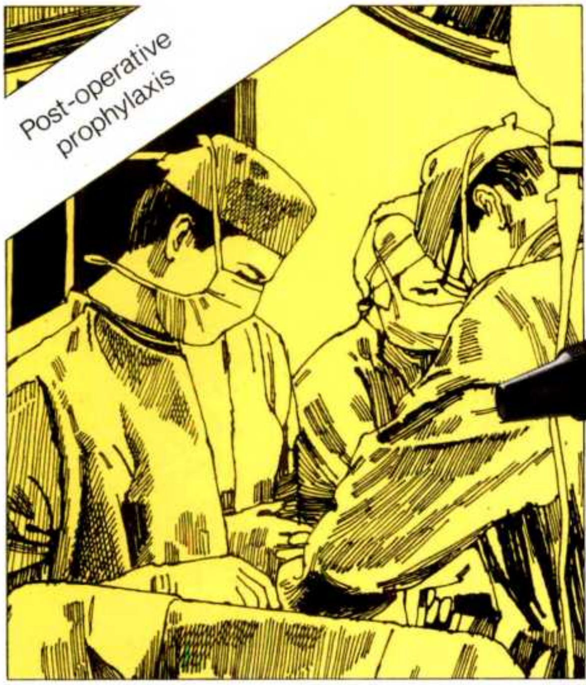

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This loss of sensitivity is due in our view to the cutting of the nerves supplying the cornea at surgery. Ruben[7] suggests that with a 180° limbal section the sensitivity recovers to a certain extent with time. Our data fail to show any correlation between the time elapsed since surgery and decreased CTT (r=+0·17). However, only the central corneal sensitivity was measured, and most of the decrease in sensitivity present would be in the upper zones of the cornea. This does not mean that central recovery is not present, as other parameters may mask this trend: (*a*) most cases had undergone surgery only recently (within less than a year); (*b*) the surgical section was variable from one eye to the other. Only a longitudinal study can elucidate these points.

There is no difference in corneal thickness between the aphakic and phakic eyes. This would suggest that if a metabolic difference exists between the 2 groups it does not affect the basal metabolism. Such a finding is not surprising, as the mean endothelial cell loss is lower than 10%, and all corneas show a density superior to 2000 cells/mm^2. Pathological corneas have been shown to maintain normal thickness and transparency with much lower density.[8]

However, Holden *et al.*[1] and Guillon and Morris[9] have shown that surgery has affected the corneal capability to respond to metabolic stress: under reduced level of oxygen the cornea of the aphakic eye swells less than in the fellow eye. Various hypotheses have been formulated to explain this phenomenon but so far with few data to support them: (*a*) Surgery has increased the endothelial permeability to lactic acid[10]; (*b*) The removal of the crystalline lens has increased the availability of certain metabolites to the endothelium, and this would offset their lack at the corneal front surface.[11]

The corneal oxygen uptake, which is an indication of the epithelial metabolism, is unchanged, showing that the epithelium fully recovers postoperatively except in those instances where endothelial failure causes stromal oedema and secondary bullous changes.[3]

Most of the monocular aphakes will need to be fitted with contact lenses to obtain single binocular vision, and several conclusions can be reached from this work. (*a*) The cornea of the aphakic eye remains less sensitive than the normal cornea. Hence these patients need to be closely monitored, as they will take longer to detect pain linked with corneal abrasion and/or infection. (*b*) Despite a basal metabolism similar to that of the normal cornea, the cornea of the aphakic eye will respond better to stress entailed by the wearing of thick lenses with low oxygen transmissibility.

We thank Professor Montague Ruben for encouraging us to carry out this work in the Contact Lens Department at Moorfields Eye Hospital and for reviewing the manuscript.

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British Journal of Ophthalmology, 1982, **66**, 524–529

Subretinal neovascularisation in ocular toxoplasmosis

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SUMMARY Subretinal neovascularisation, a common clinical pathological entity, is seen in a variety of ocular disorders. Though inflammation is associated with the development of subretinal neovascularisation, toxoplasmosis is an unusual causative agent. Two teenagers developed a disciform lesion in the macular area due to toxoplasmosis. Clinical studies revealed subretinal neovascularisation.

Toxoplasmosis is a common ophthalmic disorder and is said to cause a considerable number of cases of posterior ocular inflammation. Different investigators have considered toxoplasmosis to be the cause of 16–70% of cases of posterior uveitis.[1 2]

Subretinal neovascularisation is a clinical finding. It is seen in a variety of eye diseases, with the list of associated ocular disorders growing as fluorescein angiography has become more of a routine procedure for examining the posterior pole. In 1969 Friedmann and Knox[3] described an uncommon form of toxoplasmosis associated with macular subretinal fluid or blood. Recently 3 cases of toxoplasmosis have been reported with associated subretinal neovascularisation.[4] We wish to add to the relatively small number of these cases 2 well documented instances of ocular toxoplasmosis with subretinal neovascularisation.

Case reports

CASE 1

This was a 9-year-old girl first seen in April 1980. She had been referred by another ophthalmologist for evaluation of decreased vision in her left eye for the past 5 months. The exact time of onset of this symptom was unclear, it having first been noticed on a routine school screening. The patient was in good health, on no medications, and with no history of ophthalmic or general disease.

On initial examination her best corrected visual acuity was 20/20 OD, 20/400 OS, near vision J2 OD, J12 OS. Motility examination revealed a small left exotropia. The right pupil was normal, while the left eye had a mild amaurotic pupillary reaction. Slit-lamp examination showed a normal anterior segment bilaterally.

Fundus examination of the right eye revealed 5 discrete hypopigmented lesions with bordering pigment epithelial hyperplasia, superotemporal to the disc. The posterior pole was otherwise normal. In the left fundus a normal optic disc and vasculature were noted. The macula had a large area of retinal oedema, with a yellow-white elevated lesion, and an inferotemporal subretinal haemorrhage (Fig. 1).

Pertinent laboratory studies included a positive toxoplasmosis IFA titre of 1:256, positive adenovirus titre of 1:16, negative ascaris ELISA (enzyme-linked immunosorbent assay) and negative toxocara ELISA (CDC, Atlanta, Ga.)

A fluorescein angiogram was performed one week after initial presentation. The initial vascular phase of the left eye revealed normal major vessel filling. Most of the capillary-free zone was obscured by macular exudate. During the early arteriovenous stage at least 2 areas of lacy irregular hyperfluorescence were visible in the foveal region. With time this hyperfluorescence increased markedly. The area of haemorrhage blocked the inferotemporal aspect of the fluorescence. The lesions in the right eye appeared mildly hyperfluorescent, with surrounding blocked fluorescence—corresponding to each of the chorioretinal scars superotemporal to the disc (Figs. 2 A–D). This fluorescein angiogram was interpreted as consistent with old chorioretinal scars in the right eye and active neovascularisation with subretinal haemorrhage in the left eye.

Follow-up examination performed 8 months later showed organisation of the macular exudate, with formation of a subretinal disciform scar.

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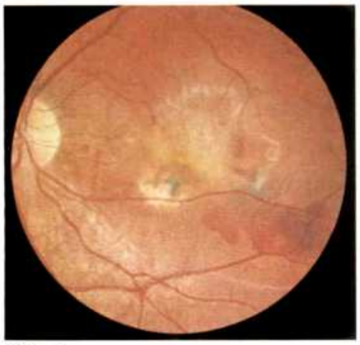

Fig. 1

Fig. 1 *Fundus photograph case 1 showing a healed pigmented scar inferiorly with subretinal haemorrhage. There are 2 foci of subretinal exudation with overlying detachment of the sensory retina.*

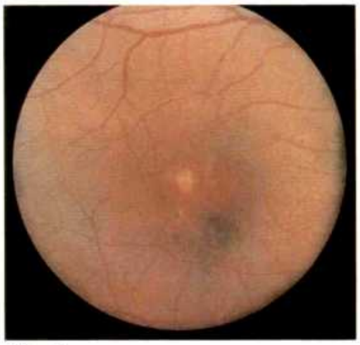

Fig. 3

Fig. 3 *Fundus photograph case 2 reveals a focus of exudation superior to fovea, with an area of pigmentation inferiorly.*

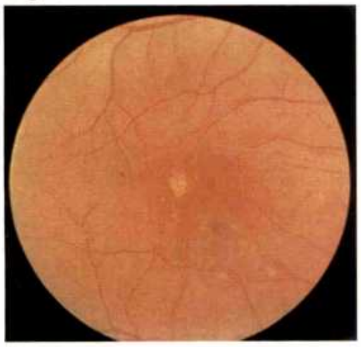

Fig. 5

Fig. 5 *Fundus photograph demonstrates the 2 lesions noted in Fig. 4, with a new exudative lesion inferior and nasal to the macula.*

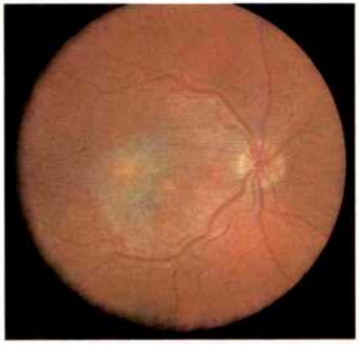

Fig. 6

Fig. 6 *Fundus photograph shows the macular area with a prominence of the new focus of exudation inferior and nasal with subretinal organisation.*

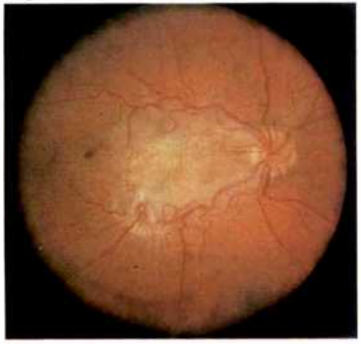

Fig. 7 *Fundus photograph demonstrates inward displacement of the inferior and superior arcades, subretinal haemorrhages, gross detachment of the sensory retina, and subretinal fibrosis.*

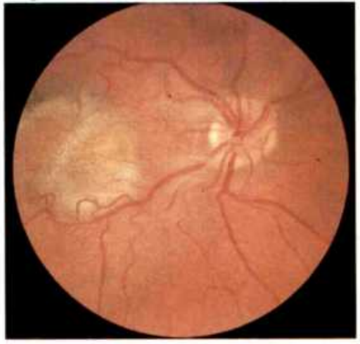

Fig. 8 *Fundus photograph shows fully developed disciform lesion.*

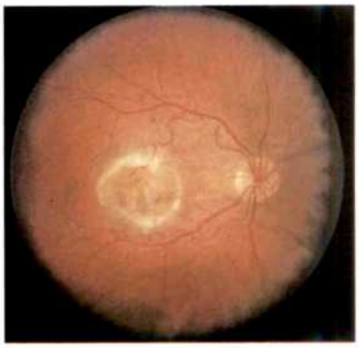

Fig. 10 *Fundus photograph reveals end-stage disciform scar.*

CASE 2

This was a 20-year-old male first seen in December 1978 by an ophthalmologist for evaluation of black spots and distorted vision in his right eye of 2 weeks' duration. He had had similar complaints 9 months earlier, which resolved spontaneously. His past medical, ophthalmological, social, and family histories all were negative except for a respiratory tract infection several months earlier.

On examination in December 1978 his best corrected visual acuity was OD 20/30, OS 20/40. The right macula was abnormal, with an area of deep linear exudation in the superior foveal region, and adjacent to this were circumscribed areas of atrophic

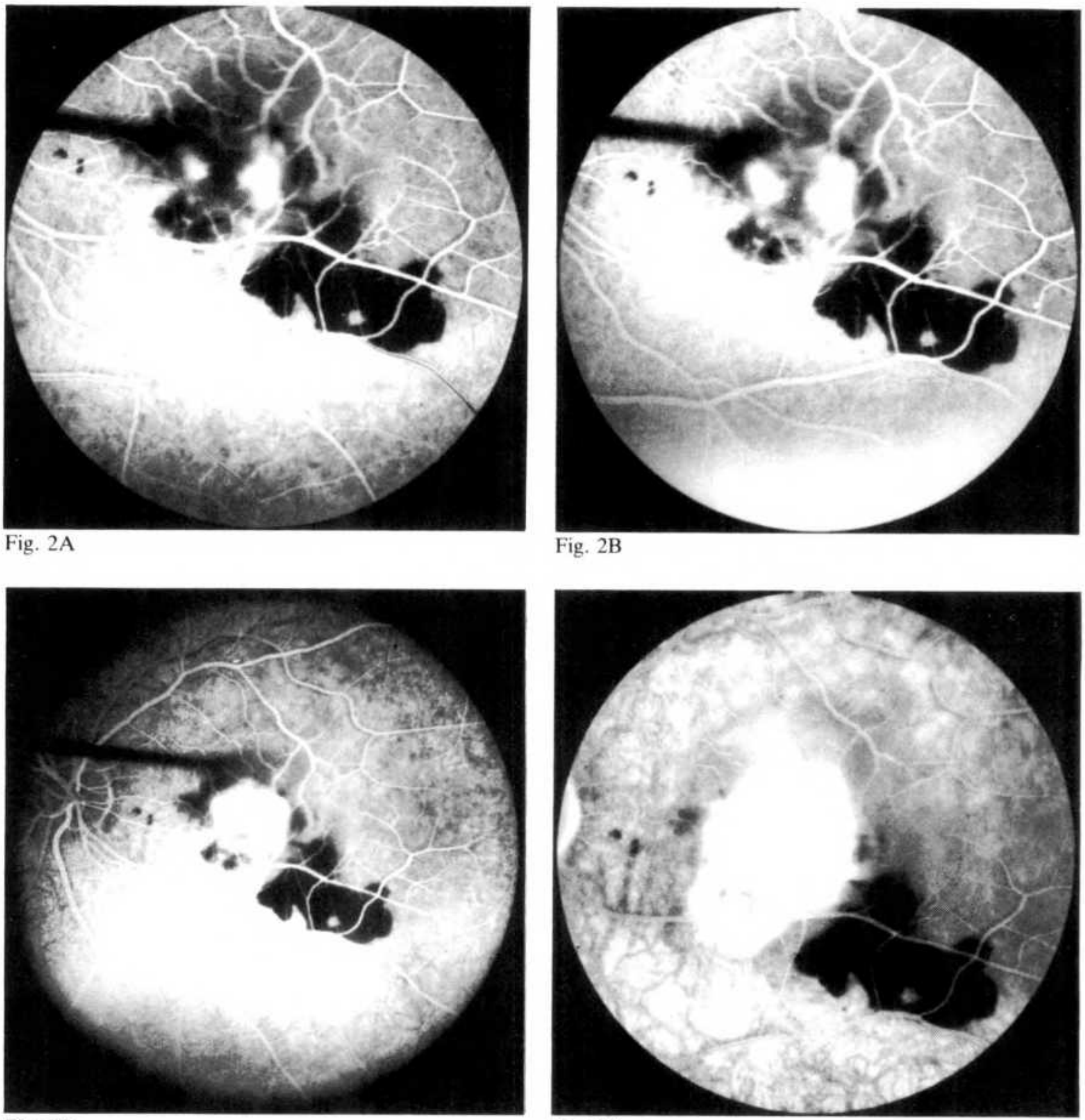

Fig. 2A

Fig. 2B

Fig. 2C

Fig. 2D

Figs. 2A,B,C,D *Fluorescein angiogram case 1 in the early arteriovenous phase* (A) *reveals 2 foci of subretinal neovascularisation with progress in* B *and* C *to form a confluent area of leakage in* D.

changes in the retinal pigment epithelium (RPE), with one area of exudation in the inferior papillomacular bundle region. The overlying vitreous had several condensations, with no true cellular reaction (Fig. 3).

A fluorescein angiogram at that time revealed localised hyperfluorescence at the areas of RPE changes, beginning at the arteriovenous phase, with little change with time. A diagnosis of retinal pigment epitheliitis was made, and the patient was started on prednisone 60 mg daily (Fig. 4).

The patient responded well to the corticosteroid therapy. At follow-up the visual acuity was 20/20 OD and he was asymptomatic. Within a month after

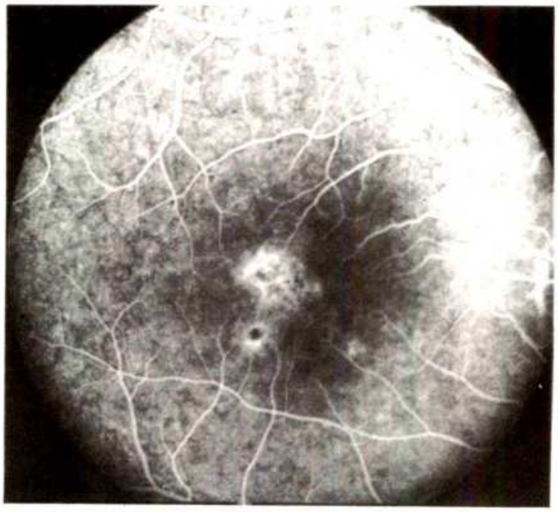

Fig. 4 *Fluorescein angiogram reveals localised hyperfluorescence at the level of the retinal pigment epithelium.*

cessation of steroid therapy he noted black spots subjectively in the right eye. They increased, and an ophthalmological examination revealed new, white, fluffy lesions in the right macula. A toxoplasmosis IFA titre at this time was 1:256.

In January 1979 the best corrected visual acuity was OD 20/40 and OS 20/20. Amsler grid testing displayed an abnormality in the right superonasal quadrant. The right anterior segment was unremarkable, while the fundus examination showed a posterior vitreous detachment, and in the macula several old healed retinal lesions and several elevated exudative lesions with surrounding retinal oedema (Fig. 5). The patient was started on therapy with prednisone 80 mg, daraprim, sulphadiazine, and folinic acid. The steroids and other medications were rapidly tapered as his acuity improved to 20/25+ OD in March 1979.

In September 1979, 6 months later, the patient returned because of recurrence of symptoms and severe visual loss in the right eye. The visual acuity OD was less than 20/200 and OS 20/20. Ophthalmoscopy revealed in the right macular area a new area of exudation with surrounding macular oedema (Fig. 6). A repeat IFA toxoplasmosis titre was 1:512. He was restarted on the previous therapy with the addition of clindamycin 1200 mg per day by mouth.

In November 1979 the macula showed a markedly distorted appearance. The superior and inferior vascular arcades were displaced toward the macula, a subretinal membrane was apparent, several subretinal haemorrhages were present temporally and inferiorly, and there was extensive serous subretinal fluid at the margins of the lesion (Fig. 7). A fluorescein angiogram performed shortly afterward showed subretinal neovascularisation with marked leakage of dye in later phases of the study (Figs. 8 and 9A and 9B).

Follow-up examination in March 1981 revealed a visual acuity of finger counting in the right eye and 20/15 in the left. The right fundus showed inward displacement of the macular arcades due to traction

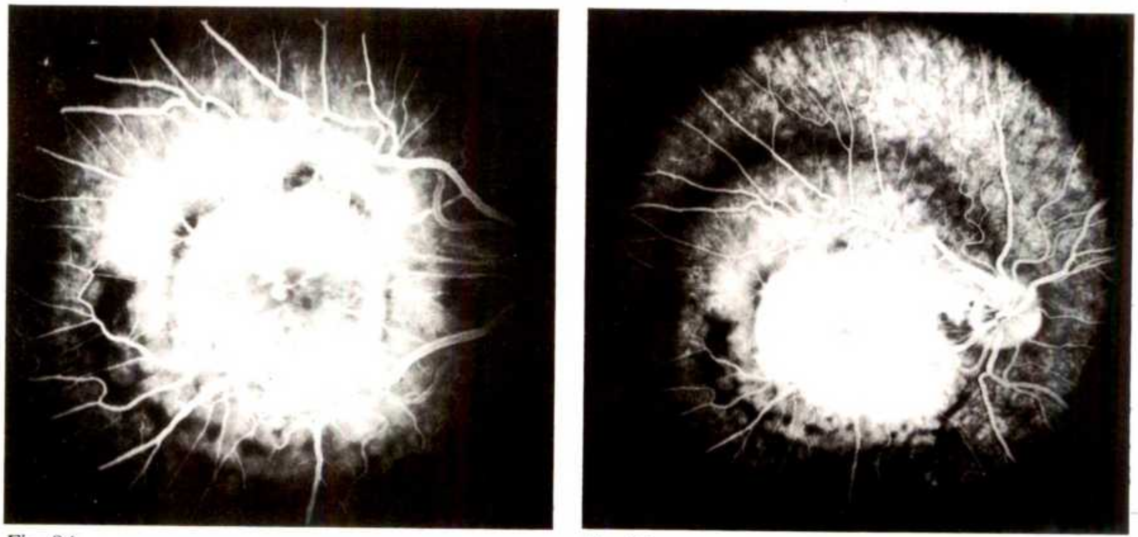

Fig. 9A

Fig. 9B

Fig. 9A,B *Fluorescein angiogram showing subretinal neovascularisation and extensive leakage.*

from the subretinal scar. There were focal areas of retinal pigment hyperplasia inferiorly (Fig. 10).

Discussion

Ocular toxoplasmosis is the local eye manifestation of a systemic infection which is due to a congenital infection that recurs later in life. The average age at the time of the first symptomatic attack is 25·3 years; the first symptoms appear between ages of 10 and 35 in 75% of the cases.[3] A high percentage of initial episodes have been noted to occur at the time of puberty. Specific attacks have been reported to last anywhere from one week to 2 years, with an average of 4·2 months per attack and an average of recurrent episodes of 2·7 per patient.[3]

Different types of active retinitis have been described clinically in toxoplasmosis.[3] The most commonly encountered lesion is the large destructive active retinitis with associated vitritis. A second type described is that of punctate inner areas of retinitis with minimal associated oedema and vitreous reaction. The third and most unusual form of toxoplasmosis has been characterised as deep retinal punctate lesions with subretinal exudate. The lesions in this group are associated with a minimal amount of vitreous reaction and with turbid subretinal fluid or blood. This group has been said to account for 0·3% of toxoplasmic lesions,[1] to be a type of disciform detachment of the retina in some ways similar to that of histoplasmosis, and always to be located in the macula or near the optic disc. Friedmann and Knox[3] suggested that the subretinal fluid present was choroidal in origin and an inflammatory response secondary to retinal disease.

Histological examination of toxoplasmic lesions reveals a retinochoroiditis with an apparent predilection of the organisms for the retina and retinal pigment epithelium. The resultant coagulative necrosis of the retina is frequently associated with underlying choroidal and scleral inflammation. Toxoplasma organisms are usually found within necrotic retinal tissues and not in the choroid.[5]

Kennedy and Wise,[6] in their case report of retinochoroidal vascular anastomosis in ocular toxoplasmosis, suggested that the formation of the anastomosis was the result of intense retinal inflammation with secondary destruction of Bruch's membrane and choriocapillaris.

The fluorescein angiographic signs of subretinal neovascularisation have been well documented and described in recent years.[7] These criteria have enabled the ophthalmologist to identify subretinal neovascular membranes, often without the aid of fluorescein angiography. In both of our cases the ophthalmoscopic picture included deep retinal haemorrhage and exudate in the macula. The fluorescein angiogram helped to confirm the clinical suspicion of subretinal neovascularisation by demonstrating the early hyperfluorescence which proceeded to detachment of the sensory retina in case 1 and subretinal scarring in case 2. In addition case 2 differs from case 1 and those described by Fine and co-workers[4] in that the neovascular membrane may well have developed during an acute or subacute infectious stage.

Table 1 *Aetiology of subretinal neovascularization**

1. Senile macular degeneration
2. Presumed ocular histoplasmosis syndrome
3. Angioid streaks
4. Choroidal rupture
5. Myopic maculopathy
6. Heredodegenerative disease (e.g., Best's, dominant drusen)
7. Optic nerve head drusen
8. Over benign choroidal tumours
9. Inflammation (e.g. toxoplasmosis)
10. Postphotocoagulation
11. Rubella retinopathy
12. Retinal and pigment epithelial hamartoma
13. Geographic helicoid peripapillary choroidopathy
14. Choroidal osteoma
15. Acute multifocal posterior placoid pigment epitheliopathy
16. Vogt-Koyanagi-Harada syndrome
17. Idiopathic

*Modified from Yannuzzi *et al.*[7]

Neither of these cases was amenable to argon laser therapy because of the central location of the subretinal neovascularisation. Conventional therapy was employed in both for treatment of the underlying condition.

In our experience we have generally found a predominance of posterior pole lesions, particularly macular, in patients with symptomatic early onset of ocular toxoplasmosis—i.e., in the second or third decade. Friedmann and Knox also found a 75% incidence of active central lesions (within 2 disc diameters of the macula) in their review of first symptomatic cases of toxoplasmosis.[3]

Subretinal neovascularisation has been generally associated with diseases of the elderly, most commonly with senile macular degeneration. Many other conditions, however, are associated with it (Table 1). It is our contention that severe macular toxoplasmosis in the young is also associated with subretinal neovascularisation and is not as uncommon as previously thought. We advise that young patients with a maculopathy possibly due to toxoplasmosis should be followed up very closely for the possible development of subretinal neovascularisation. Fluorescein angiograms should be a routine part of their examination and follow-up. Treatment, whether medical or laser, might be more effective if instituted

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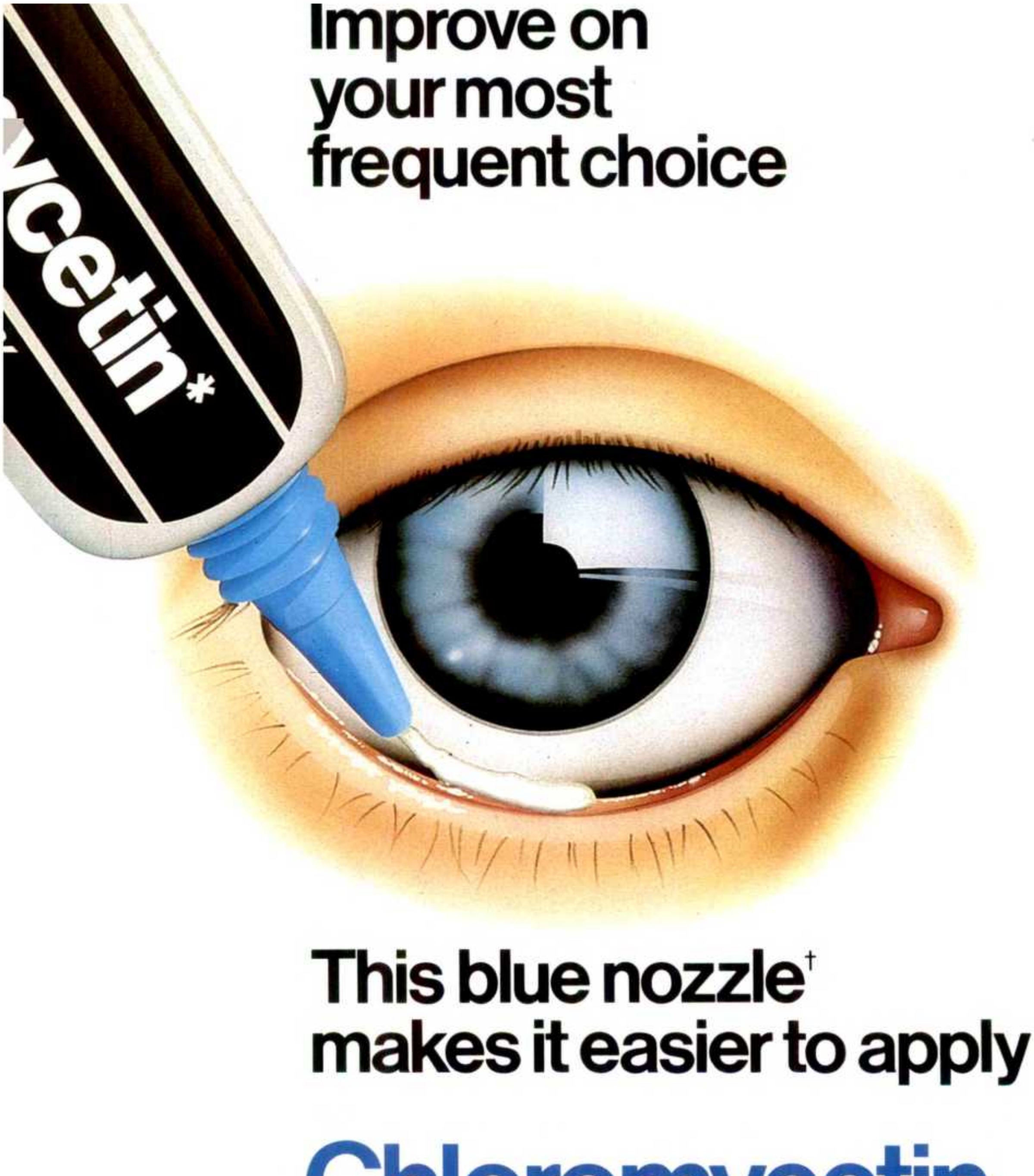

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early, prior to the development of irreversible haemorrhage and scarring.

We are indebted to Drs Stuart L. Fine, Steven M. Podos, and Robert S. Coles for their critical reviews of the manuscript, Ms Elizabeth Wilkins for secretarial assistance, and Mr Robert Campanile and Mr Howard Radzyner for the photography.

This work was supported in part by an unrestricted grant from Research to Prevent Blindness Inc.

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British Journal of Ophthalmology, 1982, **66**, 530–535

A case of macular subretinal neovascularisation in chronic uveitis probably caused by sarcoidosis

H. A. L. F. HOOGSTEDE AND A. C. COPPER

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SUMMARY A 29-year-old man with a 7-year history of bilateral chronic uveitis developed subretinal neovascularisation in the macular area of his right eye. There was a history suggesting sarcoidosis. Long-term therapy with systemic corticosteroids decreased the activity of the uveitis, and the subretinal neovascularisation changed into a cystic scar. After the systemic corticosteroids were discontinued there was a recurrence of the uveitis but not of the subretinal neovascularisation.

Subretinal neovascularisation in young people has been reported in many diseases. In the absence of inflammatory signs in aqueous and vitreous or other specific ocular abnormalities it may be related to infection with *Histoplasma capsulatum*,[1] but the same clinical picture has been observed in populations in which histoplasmosis is relatively rare.[2 3]

Some specific causes of uveitis can be complicated by subretinal neovascularisation, but only a few reports have been delivered of subretinal neovascularisation in chronic aspecific uveitis.[4 5]

Case report

A man aged 29 years noted a sudden decrease of vision of his right eye in July 1979. Since 1972 he was known to be suffering from a bilateral chronic iridocyclitis without involvement of the posterior pole.

Medical examination in 1972 showed enlarged lymph nodes at the lung hila on chest *x*-ray. Because of a negative Mantoux reaction these changes were thought to be due to sarcoidosis. Seven months later the enlargement of the lymph nodes spontaneously regressed. No other abnormalities were found.

In July 1979 the corrected visual acuity in the right eye was 0·16 and in the left eye 0·9. Intraocular pressure measured by applanation tonometry was 13 mmHg. The aqueous of both eyes showed flare and cells, and there were some old synechiae of the iris to the lens. The lenses were clear. The vitreous showed a small number of cells and somewhat more flare in the right than in the left eye.

Funduscopy of the right eye (Fig. 1) showed a subretinal haemorrhage and a grey local elevation of the retina in the macular area. In the periphery of the retina were some lesions of the pigment epithelium resembling atrophic scars. There were also some

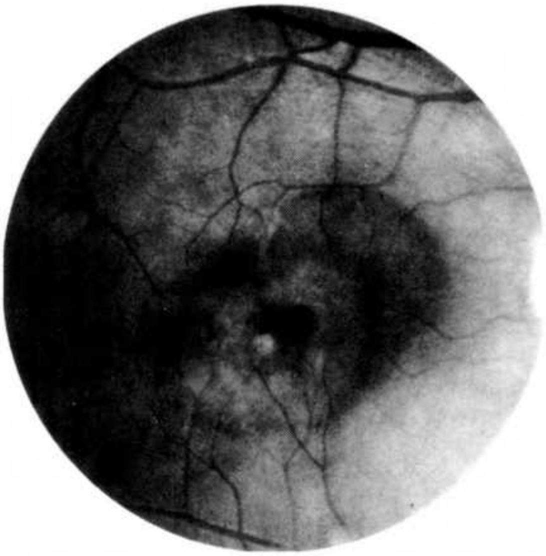

Fig. 1 *Right eye fundus photograph, showing a foveal annular dark lesion, with a small subretinal haemorrhage. The detachment of the neuroepithelium covers the whole macular area.*

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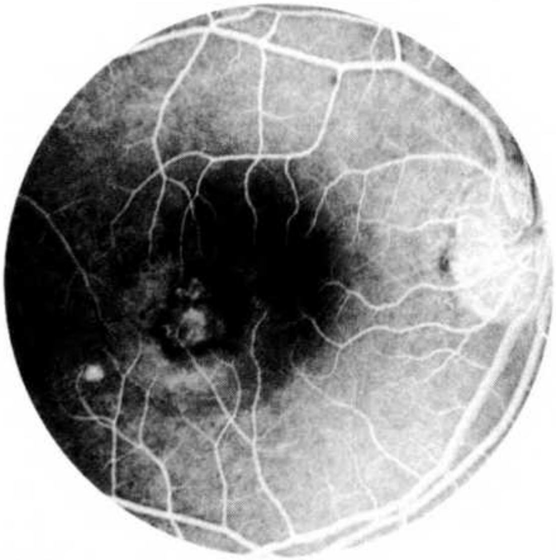

Fig. 2a

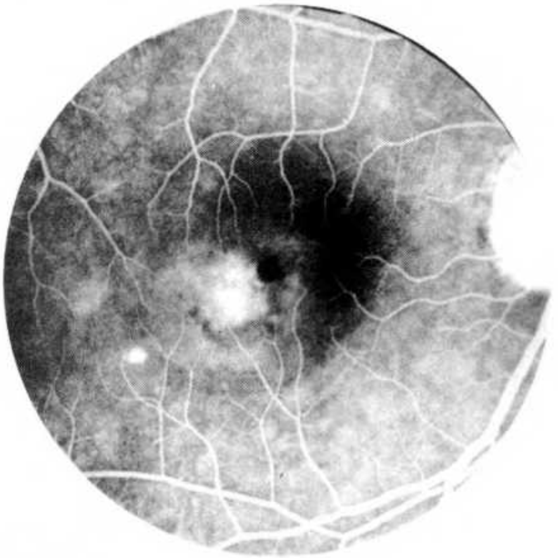

Fig. 2b

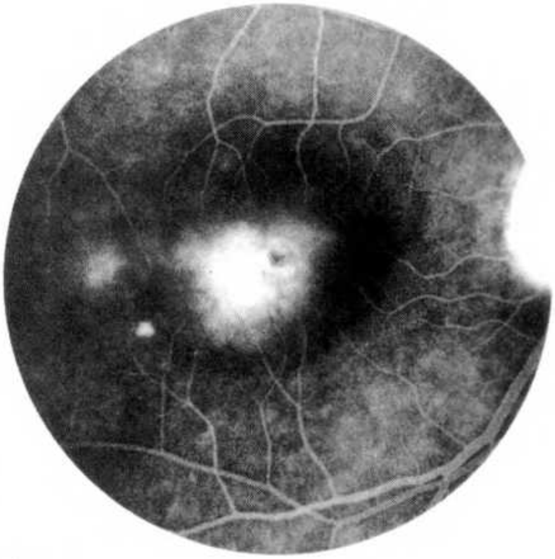

Fig. 2c

Figs. 2a,b,c *Fluorescein angiogram of the right eye.* (a) *In the early arteriovenous phase a subretinal neovascular membrane; temporal to the macular area there is a small lesion in the pigment epithelium.* (b) *Leakage from the neovascular membrane in the venous phase.* (c) *A pronounced leakage in the very late phase, and there is some leakage beneath the neuroepithelium detachment. The temporal pigment epithelial lesion shows some fluorescein staining.*

round preretinal opacities in the vitreous. No signs of typical candle-wax dripping or vasculitis were present.

Funduscopy of the left eye showed a mild superficial macular oedema and also some peripheral scars in the epithelium. There were no local vitreous opacities or signs of vasculitis.

The fluorescein angiogram of the right fundus (Fig. 2) showed a pattern of active subretinal neovascularisation and a subretinal haemorrhage with a large overlying detachment of the neuroepithelium. In addition there was some leakage at the optic disc and a small lesion in the pigment epithelium next to the macula.

An angiogram of the left fundus (Fig. 3) showed a mild cystoid oedema in the macular area, with some leakage at the optic disc.

Renewed examination showed that the erythrocyte sedimentation rate, the serum electrolytes, and the haemoglobin level were all within normal limits. Liver and kidney functions were normal, as were the

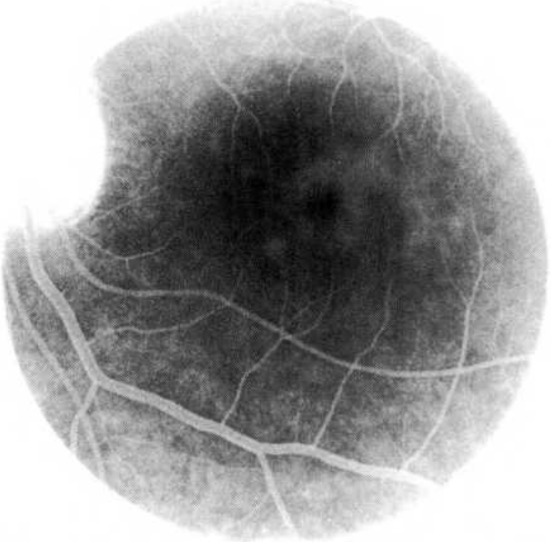

Fig. 3 *Late phase of the angiogram of the left eye, showing a mild superficial leakage in the macular area and a hyperfluorescence of the optic disc.*

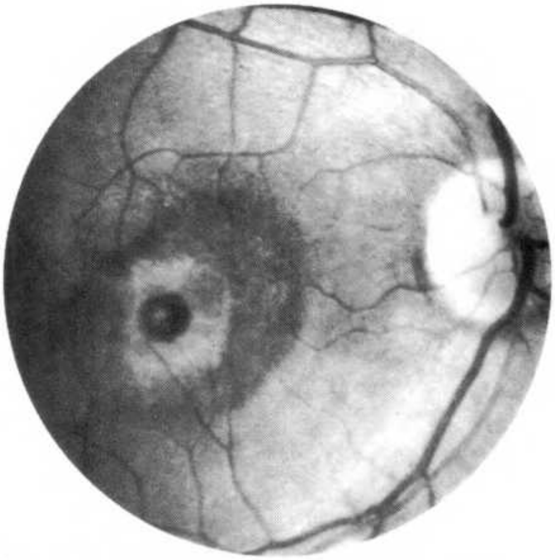

Fig. 4 *Fundus photograph of the right eye showing a central dark cyst, surrounded by annular alterations of the pigment epithelium.*

serum levels of calcium and phosphate. Tests for rheumatoid factor, antinuclear body, and toxoplasmosis serology were negative. The antistreptolysin titre was 275 U. *X*-rays of the chest, skull, and sinuses showed no abnormalities. The Mantoux reaction and the skin test for histoplasmosis were negative.

Because of the signs of active uveitis, the superficial macular oedema, and the history of a possible sarcoidosis the patient was treated with systemic

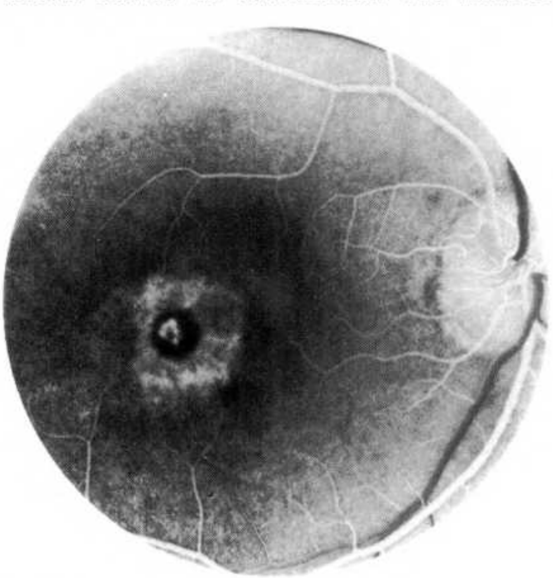

Fig. 5a

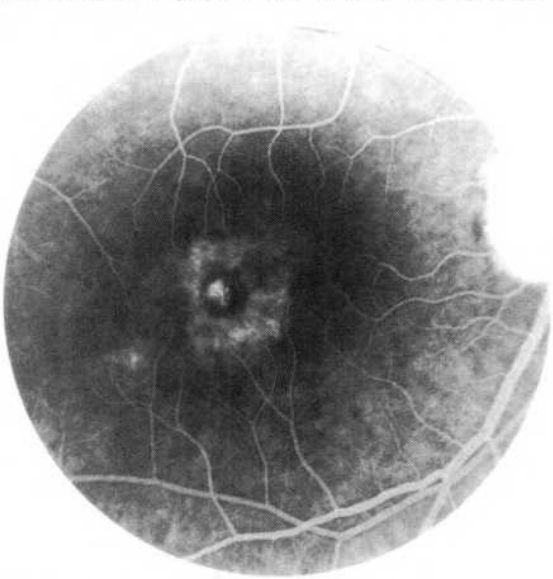

Fig. 5b

Figs. 5a,b *Fluorescein angiogram of the right eye.* (a) *In the early arteriovenous phase a central hyperfluorescent lesion, surrounded by a hypofluorescent ring. There are no signs of active subretinal neovascularisation. The alterations at the pigment epithelium resemble window effects.* (b) *In the late phase no pronounced leakage in the macular area.*

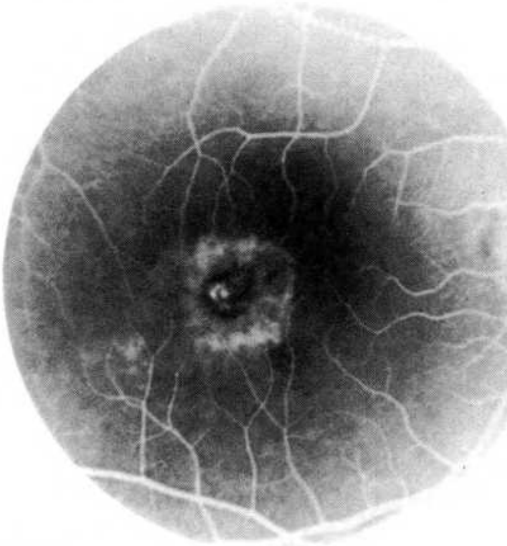

Fig. 6a

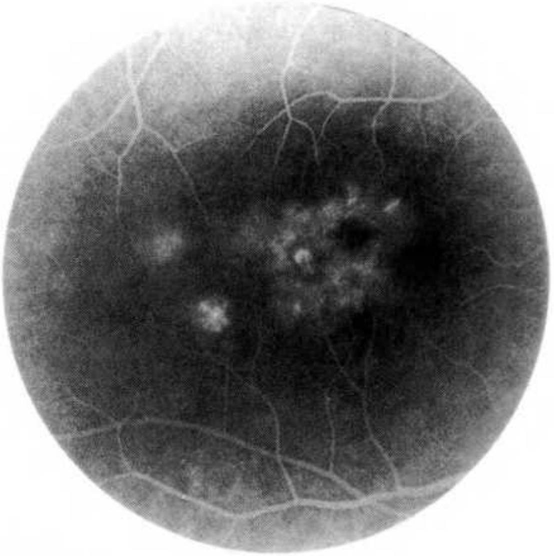

Fig. 6b

Figs. 6a,b *Fluorescein angiogram of the right eye.* (a) *An early hyperfluorescence also in the central dark lesion. No signs of active subretinal neovascularisation.* (b) *In the late phase a merely superficial leakage over the macular area, but no leakage from deep layers, except from the lower temporal lesion located in the pigment epithelium.*

corticosteroids, initially with 60 mg prednisone dd. Within 8 weeks the dosage was lowered to 20 mg d.d. and this level was maintained for some months.

Six months later the corrected visual acuity of the right eye had increased to 0·9 and of the left eye to 1·2. At that time there were no cells in the aqueous and only a mild flare in the vitreous. The macular lesion in the right eye (Fig. 4) had changed into a grey cystic scar without haemorrhage, and on the fluorescein angiogram (Fig. 5) the signs of activity of the subretinal neovascularisation had disappeared. In the left macular area a very mild superficial oedema remained. The systemic corticosteroids were gradually reduced and finally discontinued.

Ten months later there was an exacerbation of the uveitis in both eyes, with cells and flare in the aqueous and vitreous, and also a rise of intraocular pressure to 30 mmHg. The corrected visual acuity was 0·5 in the right eye and 0·8 in the left eye. The patient now refused treatment by systemic corticosteroids. For this reason only local corticosteroids in combination with antiglaucoma therapy were given.

A fluorescein angiogram of the right eye (Fig. 6) showed no activity of subretinal neovascularisation; only a cystic scar with surrounding pigment epithelium changes was visible. There was, however, some increase of the superficial macular oedema in both eyes (Fig. 7) and also some leakage at the optic discs.

Five months later the intraocular pressure was normal again, and there were minimal cells and flare in the aqueous and vitreous of both eyes. The macular lesion in the right eye did not change, and the

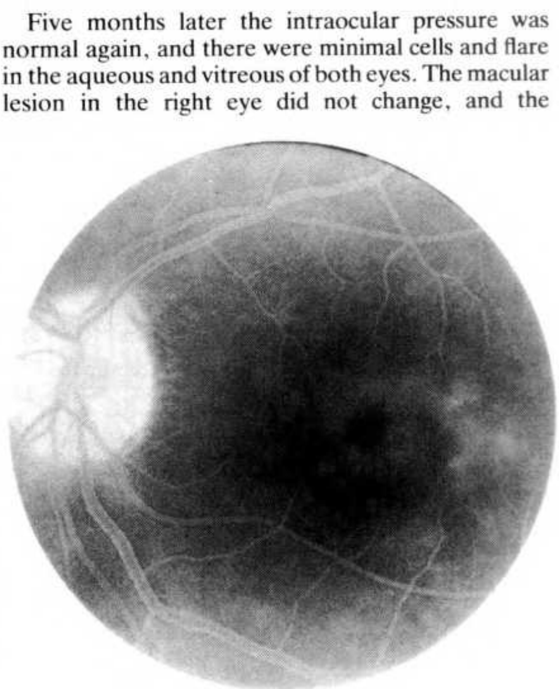

Fig. 7 *Fluorescein angiogram of the left eye shows in the very late phase only a superficial macular leakage. The optic disc is hyperfluorescent.*

corrected visual acuity had now increased to 0·8 in the right and 0·9 in the left eye. Only local corticosteroids were given, and up to September 1981 the findings did not change.

Discussion

The occurrence of subretinal neovascularisation is probably related to changes in the pigment epithelium-Bruch's membrane-choriocapillaris complex. The nature of the primary stimulating factors is not known. Ischaemia of the choriocapillaris (especially in the macular area), changes and breaks in Bruch's membrane, detachment of the pigment epithelium, haemorrhage, or other vasoproliferative factors could play a role in the stimulation of new vessel growth from the choroid into the subpigment epithelial space. Generally, subretinal neovascularisation occurs in the absence of inflammatory signs, such as in senile disciform macular degeneration,[6] angioid streaks occurring in pseudoxanthoma elasticum, Ehlers-Danlos disease, Paget's disease of the bone, sickle-cell disease, the hereditary form of senile elastosis and acromegaly,[6 7] myopia,[8] vitteliform macular degeneration,[9] hereditary drusen,[10] Sorsby's pseudoinflammatory dystrophy,[11] fundus flavimaculatus,[12] traumatic choroidal rupture,[6] focal macular choroidopathy,[3] idiopathic subretinal neovascularisation,[13] optic drusen,[14] papilloedema by pseudotumor cerebri,[15] following laser therapy,[6] and in association with choroidal naevi and tumours.[7]

On the other hand it is known that subretinal neovascularisation occurs in mainly 'inflammatory' diseases such as Behçet's disease,[16] toxoplasmosis,[17 18] toxocara,[19] serpiginous choroiditis,[20] chronic uveitis,[4 5] Harada's disease,[21] presumed sarcoidosis,[22] rubella retinopathy,[23] and presumed histoplasmosis.[1]

Fluorescein angiography is indispensable for detecting subretinal neovascularisation in the early stages. In the later stages, when there are subretinal haemorrhages or a more pronounced disciform lesion, an angiogram is not always necessary.

Subretinal neovascularisation is not a well recognised complication in chronic uveitis. This could be partly explained by the fact that some complications in chronic uveitis make it difficult to obtain a good fluorescein angiogram—for example, posterior synechiae of the iris, resulting in insufficient mydriasis, complicating cataract or vitreous opacities.

Fundus changes have often been described in sarcoidosis, including neovascularisation of the retina and optic disc.[24] Subretinal neovascularisation in patients with presumed sarcoidosis was recently reported.[22] In our patient a history of sarcoidosis was suggested but was not proved histologically.

Our case supports the concept that the appearance of subretinal neovascularisation in chronic uveitis is not mere coincidence. The disturbance of the pigment epithelium-Bruch's membrane-choriocapillaris complex in the macular area caused by uveitis may give rise to the formation of subretinal neovascularisation. Ophthalmoscopically this can develop into a lesion with the aspect of the 'focal macular choroidopathy,' 'presumed histoplasmosis,' and the like.

If special attention is given to this aspect—especially to the minor forms—more cases of this type of subretinal neovascularisation in chronic uveitis may be found.

We thank Ms H. J. H. Schenk and Mr P. van Nigtevecht, who made the photographs.

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British Journal of Ophthalmology, 1982, **66**, 536–540

Corticosteroid-induced ocular hypertension. I. Prevalence in closed-angle glaucoma

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SUMMARY Forty-eight eyes with closed-angle glaucoma and 31 eyes at risk were subjected to corticosteroid provocative tests. 65% and 9·7% respectively responded with a change in pressure $\geq$6 mmHg. The responses of the 2 groups were compared with each other and also with the corticosteroid pressure response in normal eyes. The differences in behaviour between the eyes with closed-angle glaucoma and eyes at risk, and the eyes with closed-angle glaucoma and normal eyes, are statistically highly significant. The implications of this are discussed. The prevalence of corticosteroid-induced ocular hypertension in closed-angle glaucoma is higher than previously reported.

Corticosteroid-induced ocular hypertension is a well recognised entity which has been demonstrated and reported by several observers in patients with primary open-angle glaucoma, their siblings and children, and in glaucoma suspects and apparently normal individuals.[1–11]

There are few published data on the corticosteroid response of patients with closed-angle glaucoma.[12–14] This study investigates the prevalence of corticosteroid pressure response in 2 groups of eyes related to closed-angle glaucoma.

Material and methods

Two groups of eyes were subjected to corticosteroid provocative testing.

Group A consisted of 48 eyes that had sustained closed-angle glaucoma and had been treated by peripheral iridectomy at least 6 months before the beginning of the study. The types of closed-angle glaucoma sustained were classified into chronic, acute, and intermittent.

Six out of the 48 eyes required antiglaucoma therapy to control the intraocular pressure, and the pressures had been well controlled with the same treatment (drops only) for at least 6 months without any change. The antiglaucoma therapy was continued without change throughout the corticosteroid provocative test.

Group B consisted of 31 eyes at risk of developing closed-angle glaucoma (because the fellow eyes had had a spontaneous episode of closed-angle glaucoma). These eyes were admitted into the study only if they satisfied the following criteria: (1) prophylactic peripheral iridectomy performed with an uneventful postoperative period at least 6 months prior to start of study; (2) contralateral eye had a spontaneous episode of closed-angle glaucoma; (3) open angles as assessed by a slit beam and also gonioscopically; (4) no peripheral anterior synechiae; (5) no pseudoexfoliation of the lens capsule; (6) no significant amount of pigment in angles; (7) normal discs; (8) normal visual fields—central and peripheral; (9) intraocular pressure by applanation, outflow facility, and Po/c ratio all within normal limits; (10) patient not on oral hypotensive agent, namely, acetazolamide.

CORTICOSTEROID PROVOCATIVE TEST

This was performed as follows.

1. Patient education: (*a*) risks of test; (*b*) importance of 100% compliance. Patients were asked to keep a record of missed drops. Those who missed 24 out of a total of 168 administrations over a 6-week period (equivalent to missing one day's administration/week) were judged to have complied poorly, and the test therefore to be invalidated if negative.
2. Pretest detailed examination of the eye for best visual acuity, herpetic corneal disease, pupillary

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Table 1 *Features of the samples*

		Closed-angle glaucoma eyes	*Eyes at risk*
Total no. of eyes		48	31
No. of patients		41	31
Bilateral cases		7	—
Eyes provoked:	right	23	16
	left	25	15
Age range (years)		49–79	49–79
Average age of patient		67·4	69
Standard deviation		8·4	8·0
Sex:	Male	10	6
	Female	31	25
Race:	Caucasians	48	31
	Negroes	—	—
	Others	—	—

diameter, pseudoexfoliation, lens changes, ophthalmoscopy, field studies, gonioscopy for peripheral anterior synechiae and pigment, assessment of angles by the slit beam.

3. Initial applanation tonometry and tonography, time of day being noted.

4. The patients were instructed to instil, after shaking the bottle, one or 2 drops of the corticosteroid preparation into the lower fornix 4 times a day.

5. The preparation used was dexamethasone 0·1%; preservative benzalkonium chloride 0·01%; vehicle hydroxypropyl methylcellulose 0·5%; available commercially as Maxidex.

6. The patients were seen at weekly intervals at about the same time of day for applanation tonometry and tonography; on occasions after 2 weeks.

7. The test was terminated after 6 weeks with a final applanation tonometry and tonography unless a high response (intraocular pressure checked 3 times) was observed before then.

8. All provocative test resulting in or terminated because of a high response were treated with a single dose of gutt. pilocarpin. 2% to the involved eye and a single oral dose of acetazolamide (Diamox Sustet) 500 mg. The intra-ocular pressure was checked again in 24 hours. If the intraocular pressure had not returned to the pretest level or a reasonably lower pressure, the above treatment was repeated and the patient seen again after 24 hours. The probability of this happening was less than 1%.

9. The patients with a positive response were seen one or 2 weeks after termination of provocative test for a post-test examination which included best visual acuity, lens changes, ophthalmoscopy, and applanation tonometry. Field studies and tonography were done as indicated.

10. A positive corticosteroid provocative test was defined as a change in intraocular pressure greater than 5 mmHg.

Results

The features of the 2 groups studied are summarised in Table 1. The results of corticosteroid provocative tests in closed-angle glaucoma eyes and eyes at risk are shown in Tables 2 and 3 respectively.

GROUP A

The corticosteroid provocative test in the 48 eyes with closed-angle glaucoma resulted in a 65% positive response: 50% (i.e., 24 eyes) had an intermediate response (a change in intraocular pressure (ΔP) of 6–15 mmHg) and 15% (i.e., 7 eyes) a high response ($\Delta P \geq 16$ mmHg).

The type of closed-angle glaucoma sustained was

Table 2 *Results of corticosteroid provocative test in eyes of 48 patients with closed-angle glaucoma*

	Initial			*Final*			*ΔP*	*ΔC*
	P_1	C_1	*Po/c*	P_2	C_2	*Po/c*	P_2-P_1	C_2-C_1
Mean	19	0·23	102	27·4	0·19	226	+8·4	−0·04
SEM	0·48	0·01	6·8	1·17	0·02	26·7	0·86	0·01

P=intraocular pressure. C=outflow facility. Δ=change. SEM=standard error of mean.

Table 3 *Results of corticosteroid provocative test in eyes at risk of 31 patients*

	Initial			*Final*			*ΔP*	*ΔC*
	P_1	C_1	*Po/c*	P_2	C_2	*Po/c*	P_2-P_1	C_2-C_1
Mean	17·2	0·27	73	19·5	0·24	106	+2·23	−0·03
SEM	0·50	0·01	3·84	0·64	0·02	10·4	0·47	0·02

Abbreviations as in Table 2.

Table 4 *Results of corticosteroid provocative test in eyes with closed-angle glaucoma and comparison with Becker's results*

	No. of eyes provoked	*No. of positive test*	*% Responders*	*Mean ΔP (mmHg)*	*Mean ΔC*	*Mean %ΔC*
Present study						
Chronic	1	1	100%	10	−0·04	−25%
Intermittent	10	8	80%	12·2	−0·04	−26·2%
Acute	37	22	59%	7·38	−0·04	−19%
Total	48	31	65%	8·44	−0·04	−21%
Becker[12]	10	2	20%	3·9	−0·04	−19%

Abbreviations as in Table 2.

classified into chronic, acute, and intermittent. Of the 48 eyes provoked 1 had chronic closed-angle glaucoma, 37 acute closed-angle glaucoma, and 10 intermittent closed-angle glaucoma. The number of positive corticosteroid provocative tests in each of these classes was 1, 22, and 8 respectively.

The mean change in C value for each of the 3 classes of closed-angle glaucoma was −0·04. When this was considered in relation to the pretest C value, it represented a reduction in outflow facility of 25% for the eyes with chronic closed-angle glaucoma, 19% for the eyes with acute closed-angle glaucoma, and 26·2% for the eyes with intermittent closed-angle glaucoma.

The overall mean ΔP for the 48 eyes was +8·44 mmHg, and this was accompanied by an overall mean change in outflow facility (ΔC) of −0·04, a reduction equivalent to 21%.

These results are summarised in Table 4 and compared with Becker's results.[12]

GROUP B

Three of the 31 eyes at risk of developing glaucoma (9·7%) showed a positive response, 2 with a change in pressure of 6 mmHg and the third with ΔP 10 mmHg.

The mean ΔP for the 31 eyes at risk was +2·23 mmHg and the mean ΔC is −0·03, equivalent to a reduction in outflow facility of 10%.

These results are compared with Kitazawa's[14] in Table 5.

STATISTICAL ANALYSIS

Nonparametric statistical tests were employed to analyse the data on pressure change obtained from this study for the following reasons: (1) Limited knowledge about the population parameters. For example, the frequency distribution of corticosteroid pressure response is debatable. Armaly[4 20] and Becker [5 21] both observed a trimodal frequency distribution, but Schwartz *et al.*[15] found a near normal distribution with a simple skewness. (2) It is important that the conclusions from this study apply generally rather than only to a specific sample. (3) Some of the data are classificatory and therefore not amenable to analysis by the Students *t* test (4) Because the numbers are large in this study, the power of the nonparametric tests to reject the null hypothesis becomes comparable with that of the parametric tests.

The data on outflow facility are subjected to parametric statistics because there is no reason to presume that the corticosteroid-induced change in their value is in any way genetically influenced, although it has been suggested that outflow facility is genetically determined.[16]

The statistical analysis of the data from this study and the testing of the hypotheses formulated as a logical consequence of the results are summarised in Table 6.

Discussion

The prevalence of corticosteroid-induced ocular hypertension in eyes with closed-angle glaucoma is much higher than has been previously reported. 65% of the 48 eyes with closed-angle glaucoma in this study had a positive corticosteroid provocative test, and this figure approaches the percentage of responders in primary open-angle glaucoma as cited

Table 5 *Results of corticosteroid provocative test in eyes at risk of developing closed-angle glaucoma compared with results of Kitazawa's study*[12]

Eyes at risk	*No. of eyes provoked*	*No. of positive test*	*% Responder*	*Mean ΔP (mmHg)*	*Mean ΔC*	*Mean %ΔC*
Present study	31	3	9·7%	2·23	−0·03	−10%
Kitazawa[14]	15	0	0%	*	*	

*Figures not available but stated to be not statistically significant. Abbreviations as in Table 2.

Table 6 *Statistical analysis of data and hypotheses*

Parameter/hypothesis	*Statistical test*	*Level of Significance*
1. ΔP closed-angle glaucoma eyes	Wilcoxon (z=−5·84)	p<0·00001
2. ΔC closed-angle glaucoma eyes	Correlated *t* test (*t*=−4·0)	p<0·001
3. ΔP eyes at risk	Wilcoxon (z=−3·52)	p<0·0005
4. ΔC eyes at risk	Correlated *t* test (*t*=−1·50)	Not significant p>0·1
5. There is a difference in the corticosteroid pressure response in closed-angle glaucoma eyes and eyes at risk	Mann—Whitney U test (corrected for tied ranks z=6·22) cf. *t* test (*t*=5·45)	p<0·0001 p<0·001
6. There is a difference in the distribution of pressure response to corticosteroids in closed-angle glaucoma eyes and normal eyes (Armaly/Becker)	Present study *vs.* Armaly χ^2=12·11 Present study *vs.* Becker χ^2=12·2	p<0·01 p<0·01

Abbreviations as in Table 2.

by several workers—Nordmann *et al.*[1] 80%; Becker and Hahn[5] 92%; Armaly[2] 92%. Kitazawa's[14] 100% response in 10 patients with primary open-angle glaucoma is excluded because antiglaucoma therapy was discontinued 7–14 days before the corticosteroid provocative test, and the pressure change in these eyes must therefore be subject to doubt as to whether it was induced entirely by the topical corticosteroids.

The common factor to the 3 groups of eyes with closed-angle glaucoma is an angle-closing mechanism (partial angle closure). Because the presentation of acute closed-angle glaucoma is dramatic, the opportunity for further episodes of angle closure is terminated early by performing a peripheral iridectomy. It is not unreasonable to assume that patients in the other 2 groups—chronic and intermittent—will have had a prolonged episode or several episodes of partial angle closure before the diagnosis was made, because of the less dramatic mode of presentation. The inference from this is that there is a positive correlation between the episodes of partial angle closure and corticosteroid pressure response (see Table 4).

The importance of partial angle closure was given prominence by Mapstone[17–19] when he wrote, 'Acute closed-angle glaucoma is merely an incident (but an obvious one) in the evolution of a disease process that can have other more subtle consequences too.'[17] He had earlier provided evidence to support the hypothesis that intermittent partial angle closure is one of the causes of ocular hypertension[18] and had shown that partial angle closure could be demonstrated in some eyes with apparent open-angle glaucoma.[19] An obvious question from this which begs for answer is whether the high prevalence of corticosteroid response in patients with primary open-angle glaucoma and ocular hypertension is in any way related to partial angle closure. An attempt to answer this question now without justifying the inference made earlier would be most inappropriate. Suffice it to say at this stage that the answer to that question, if favourable, will be of some clinical relevance.

The inference that there is a positive correlation between the episodes of partial angle closure and corticosteroid pressure response is almost impossible to justify because the former parameter cannot be quantified. But what is amenable to experimental testing is whether eyes that have sustained a form of closed-angle glaucoma behave differently from normal eyes in their response to topical corticosteroids. The results of corticosteroid provocative tests in eyes with closed-angle glaucoma from this study are compared with Armaly's and Becker's results in normal eyes in Table 7. There is a highly significant difference (p<0·01) in the distribution of corticosteroid pressure response as shown in Table 6, no. 6, and this can be attributed to the closed-angle glaucoma. The alternative explanation is that both closed-angle glaucoma and corticosteroid pressure

Table 7 *Comparison of corticosteroid response in closed-angle glaucoma eyes and normal eyes*

Study	*Number*	*Parameter*	*Low*	*Intermediate*	*High*
Present study (closed-angle glaucoma eyes)	48		17 (35%)	24 (50%)	7 (15%)
vs.		ΔP			
Armaly[20] (normal eyes)	80		53 (66%)	23 (29%)	4 (5%)
Present study (closed-angle glaucoma eyes)	48		10 (21%)	21 (44%)	17 (35%)
vs.		FP			
Becker[21] (normal eyes)	50		35 (70%)	13 (26%)	2 (4%)

ΔP=change in pressure. FP=final pressure.

response could be due to a third common factor.

The corticosteroid pressure response in the 31 eyes at risk is in close agreement with Kitazawa's result in 10 patients, and the percentage of responders is similar to that reported for normal eyes by some observers.[6] Comparing this with the response in closed-angle eyes in this study (see Table 6, row 5) we find a highly significant difference ($p<0\cdot0001$).

From these comparisons it becomes apparent that eyes with closed-angle glaucoma behave differently from normal eyes and eyes at risk in their pressure response to topical corticosteroids. Because of the nature of the samples used in testing this hypothesis, the genetic influence on the high prevalence of corticosteroid-induced ocular hypertension in eyes with closed-angle glaucoma (65%), and on the highly significant difference in response when compared with normal eyes and eyes at risk, cannot be properly assessed and eliminated. Yet because of the clinical significance of this hypothesis it is important that the genetic influence be eliminated. This can be done simply by using matched pairs of eyes which are provided by patients with unilateral closed-angle glaucoma. Any difference between the paired eyes would be a reflection of the effect of the closed-angle glaucoma and not of the genetic composition of the patient, as this will be common to both eyes. This is the subject of the second part of this paper. Armaly[2] used this experimental model in 1967 but with respect to traumatic angle recession glaucoma in 11 patients. He concluded that the response to topical dexamethasone did not reflect the local changes in the glaucomatous eye but the genotype of the patient.

The following conclusions are drawn: (1) The prevalence of corticosteroid-induced ocular hypertension in closed-angle glaucoma eyes is higher than previously reported. (2) Eyes at risk of developing closed-angle glaucoma (because the fellow eyes had spontaneous closed-angle glaucoma) have a much lower prevalence of positive corticosteroid pressure response. (3) There is a marked difference between the corticosteroid pressure response of eyes with closed-angle glaucoma and normal eyes or eyes at risk.

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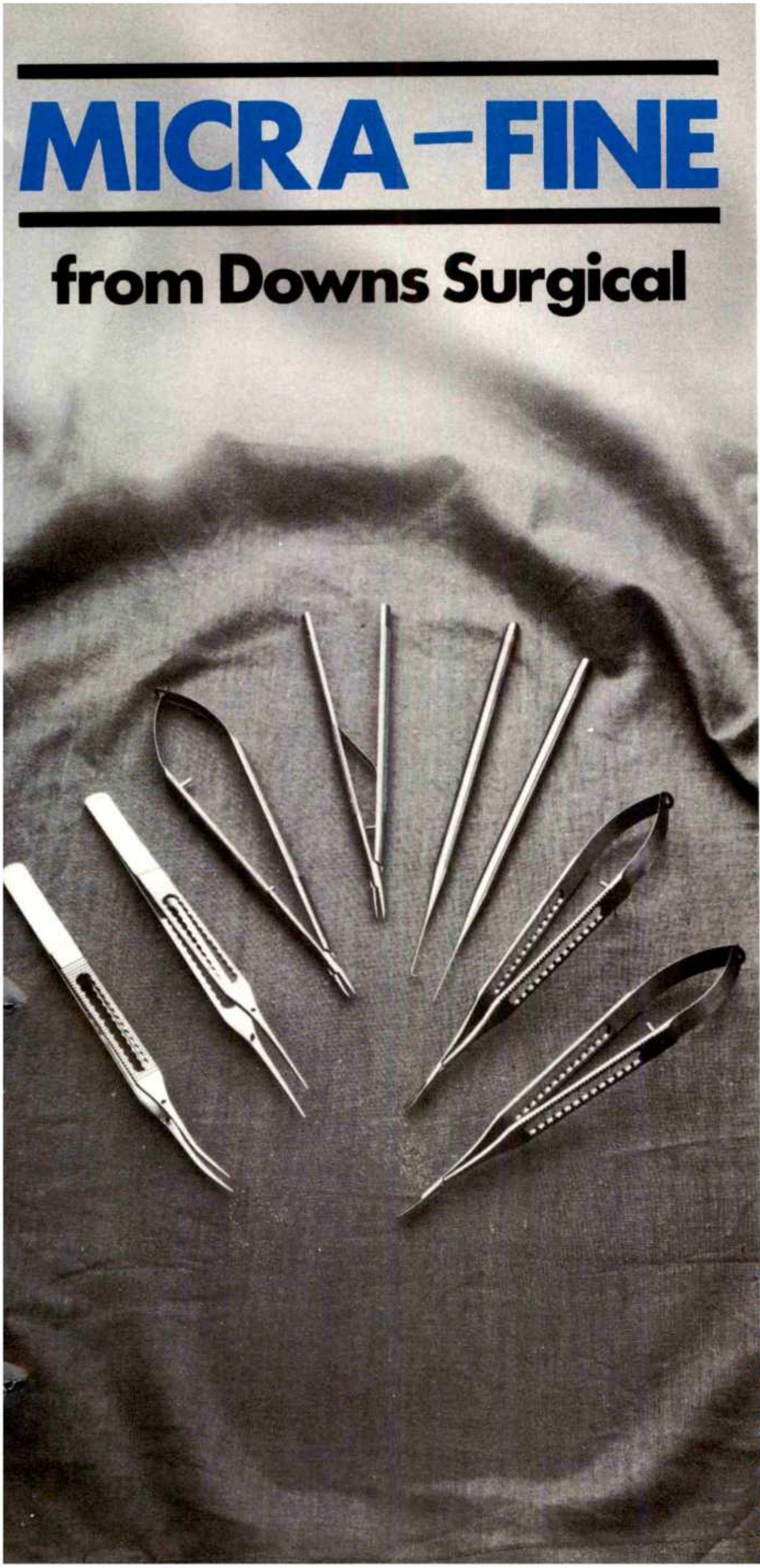

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Corticosteroid-induced ocular hypertension. II. An acquired form

SUMMARY Thirty-five patients with unilateral closed-angle glaucoma treated by peripheral iridectomy and prophylactic peripheral iridectomy in the fellow eyes were subjected to corticosteroid provocative test in both eyes. 51% of the eyes with closed-angle glaucoma and 11% of their fellow eyes had a positive corticosteroid pressure response. The closed-angle glaucoma eyes and their fellow eyes responded differently as shown by the frequency distribution graphs and also by the difference between the corticosteroid-induced change in pressure (Wilcoxon test, $z=-4.80$, $p<0.0001$). These results provide evidence for an acquired form of corticosteroid-induced ocular hypertension and the possible pathogenic factors for the first time. The clinical significance of an acquired form of corticosteroid-induced ocular hypertension is discussed.

Ever since the conception of corticosteroid-induced ocular hypertension was advanced by François[1] in 1954 the subject has been extensively studied and widely reported. In the 2 decades following François's paper reports on further observations, ideas on pathogenesis, the genetic influence, clinical significance, and the prognostic and investigative value of the corticosteroid pressure response have appeared.[2–10] Notable among these early reports were those by Armaly[7–9] and by Becker and coworkers,[10–12] which led to the hypothesis that corticosteroid-induced ocular hypertension was inherited as a single-gene autosomal trait and that it was intimately related to the inheritance of primary open-angle glaucoma. This basic premise, if correct, was supposed to transform the corticosteroid provocative test into a valuable predictive and diagnostic tool in screening patients for primary open-angle glaucoma. It would also help to select those glaucoma suspects who require treatment because of a definite risk of progression to glaucoma.[6] The potential of such a test and its status in clinical ophthalmology were never realised, and other observers started to question the validity of the monogenic hypothesis.[5 13 14]

Evidence to support an acquired form of corticosteroid-induced ocular hypertension is here presented. The possible pathogenic factors in the production of such an acquired response are identified and discussed.

Material and methods

A corticosteroid provocative test, as described in the first part of this paper, was performed on patients attending the outpatient clinics who had sustained a spontaneous episode of closed-angle glaucoma in *only* one eye and been treated initially with a peripheral iridectomy with or without supplementary medical therapy. All these patients had been operated on at least six months previously, and those on supplementary medical therapy had been on the same treatment for at least 6 months without any change and with normal intraocular pressures. The fellow eyes in all these patients showed no evidence of a previous episode of closed-angle glaucoma, though 5 of them had a positive phenylephrine-pilocarpine provocative test (nos. 8, 16, 19, 24, 35). All the fellow eyes had been subjected to prophylactic peripheral iridectomies.

Patients excluded from this study include (a) those on systemic steroids or carbonic anhydrase inhibitors; (b) those who proceeded to have a drainage operation following the initial peripheral iridectomy.

The sample consisted of 35 patients, all Caucasians, 8 males and 27 females, aged 49–80 years (average 68·5 years, SD 8·22). The episode of closed-angle glaucoma occurred in the right eye in 18 patients and in the left eye in 17. Six patients were on supplementary medical therapy. Sixteen had significant peripheral anterior synechiae ranging from 10% to 60% (mean 26%, SEM 3·23), and 8 had a significant amount of pigment in the angle.

Results

The corticosteroid-induced pressure changes in the eyes with closed-angle glaucoma and their fellow eyes are shown in Table 8. 51% (18 out of 35) of the closed-angle glaucoma eyes responded to the topical

Table 8 *Results of corticosteroid provocative testing*

	Close-angle glaucoma eyes (CAGE)		*Fellow eyes (FE)*		*Δ P CAGE–Δ PFE*
	Δ P	*Δ C*	*Δ P*	*Δ C*	
Mean	+7·26	−0·02	+2·43	−0·02	+4·83
SEM	1·09	0·02	0·54	0·02	0·81

Δ *P*=Change in pressure (mmHg). Δ *C*=change in outflow facility. SEM=standard error of the mean.

dexamethasone with a change in pressure greater than 5 mmHg, whereas only 11% (4) of their fellow eyes had a change in pressure greater than 5 mmHg. The 4 patients with a positive response in the fellow eyes also showed the greatest response in their closed-angle glaucoma eyes.

Figs. 1 and 2 show the frequency distributions of the intraocular pressures in the eyes with closed-angle glaucoma and the fellow eyes respectively, before and after the corticosteroid provocative testing. The distributions of the initial pressures (pretest) in both groups of eyes were near normal. The mean initial pressure in the closed-angle glaucoma eyes was 18·11 mmHg (SEM 0·54, variance 10·04). The mean initial pressure for the fellow eyes was 17·03 mmHg (SEM 0·47, variance 7·46).

The distribution of the post-test intraocular pressure (final pressure) in the fellow eyes retained the general outline of a Gaussian curve but with a positive skew (Fig. 2). A more representative picture is obtained by using change in pressure as the parameter for corticosteroid-induced ocular hypertension, and Fig. 3 illustrates the frequency distribution of the corticosteroid-induced pressure change in the fellow eyes. The distribution remained near Gaussian with a positive skew.

The frequency distribution of the final pressures in the eyes with closed-angle glaucoma is shown in Fig. 1 and the frequency distribution of the corticosteroid-induced change in pressure in the same eyes is illustrated by Fig. 4.

A final graphic analysis is employed to compare and contrast the frequency distributions of the corticosteroid-induced pressure change in the fellow eyes and the eyes with closed-angle glaucoma and also to assess the conformity of the observed distributions already (Figs. 3 and 4 respectively) to a Gaussian or multimodal distribution. Figs. 5 and 6 illustrate the percentage cumulative frequency plotted along a probability ordinate scale constructed so that a Gaussian distribution would appear linear. The percentage cumulative frequency distribution of

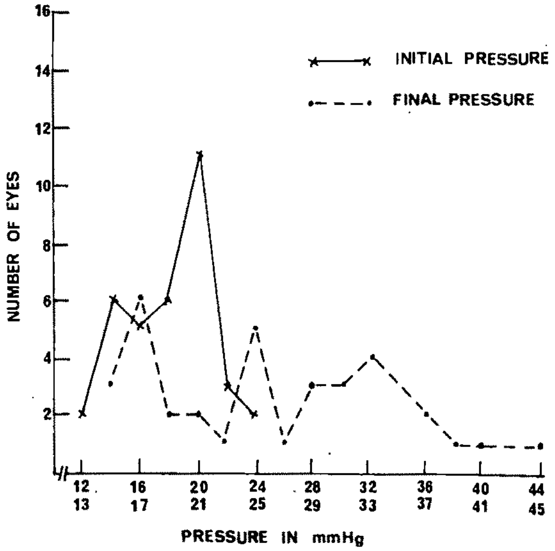

Fig. 1 *The frequency distributions of the initial pressures and the final pressures following corticosteroid provocative tests in eyes with closed-angle glaucoma.*

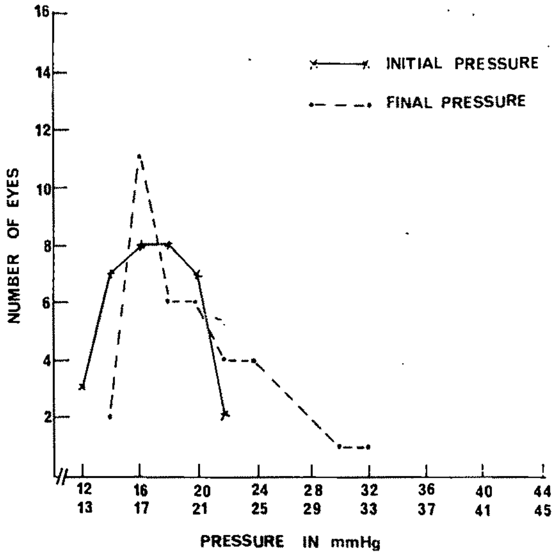

Fig. 2 *The frequency distribution of the initial pressures and final pressures following corticosteroid provocative tests in the fellow eyes.*

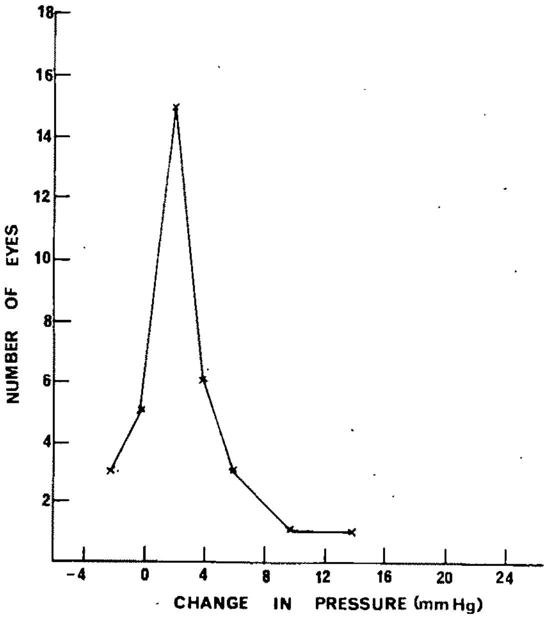

Fig. 3 *Frequency distribution of corticosteroid-induced change in pressure in fellow eyes.*

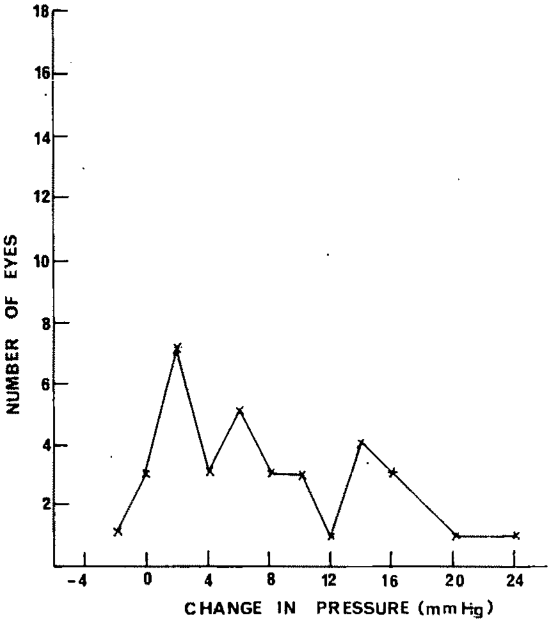

Fig. 4 *Frequency distribution of corticosteroid-induced change in pressure in closed-angle glaucoma eyes.*

the corticosteroid-induced changes in pressure in the fellow eyes is shown in Fig. 5. The graph is curvilinear, implying that the distribution of the pressure change in the fellow eyes is not a simple Gaussian curve, but it distinctly lacks the inflections which would suggest multimodality. The corresponding graph for the eyes with closed-angle glaucoma (Fig. 6) on the other hand shows these inflections rather convincingly.

The difference between the corticosteroid pressure response of the paired eyes of each patient (one closed-angle glaucoma eye and its clinically normal fellow eye) is calculated and shown in the last column of Table 1. There is a highly significant statistical difference between the corticosteroid-induced change in pressure in the matched pairs of eyes (Wilcoxon test, z=−4·80, p<0·0001). The difference in change in pressure in each pair is greater than 5 mmHg in 46% of the patients.

Discussion

The mean initial pressure for the eyes with closed-angle glaucoma (18·11 mmHg) is significantly higher (p=0·02, *t* test) than the mean initial pressure for the fellow eyes (17·03 mmHg), but there is no significant difference in the relative dispersion of the initial pressures in the 2 groups (p>0·05, F test). This implies that the closed-angle glaucoma eyes and their fellow eyes before the corticosteroid provocative test constitute a homogeneous population, that is, the 2 samples are from the same population. The fact that clinically normal eyes after an attack of closed-angle glaucoma show a significant increase in intraocular pressure relative to the fellow eyes was reported by Mapstone.[15]

Because the number of patients in the sample in this study is relatively small, the interpretation of the graphic illustrations must be made with caution. Firstly, the percentage cumulative frequency distribution of the change in pressure in the fellow eye (Fig. 5) does not show the multimodality expected with the hypothesis of simple monogenic inheritance as proposed by Armaly[7–9] and Becker *et al.*[10–12] Secondly, the frequency distribution of the final pressures in the closed-angle glaucoma eyes (Fig. 1) and the frequency distribution of the corticosteroid-induced pressure change in the eyes with closed-angle glaucoma (Fig. 4) are different from the corresponding graphs for the fellow eyes in 2 ways: (*a*) there is a much wider scatter of the abscissa points—for example, the final pressures have a variance of 64·12 compared with 16·48 for the fellow eyes; (*b*) the 2 graphs appear to have more than a single mode. This is confirmed by the inflections in Fig. 6.

These results reinforce an earlier observation that eyes that have sustained a spontaneous episode of closed-angle glaucoma respond differently to topical corticosteroids when compared with clinically normal eyes, but also, by the use of matched pairs of eyes, they allow us to dismiss any influence the genotype of the

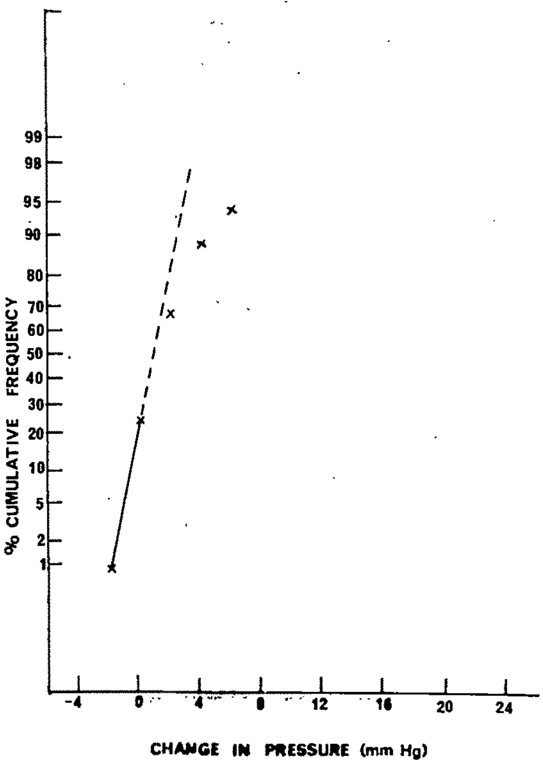

Fig. 5 *Percentage cumulative frequency distribution of corticosteroid-induced change in pressure in fellow eyes.*

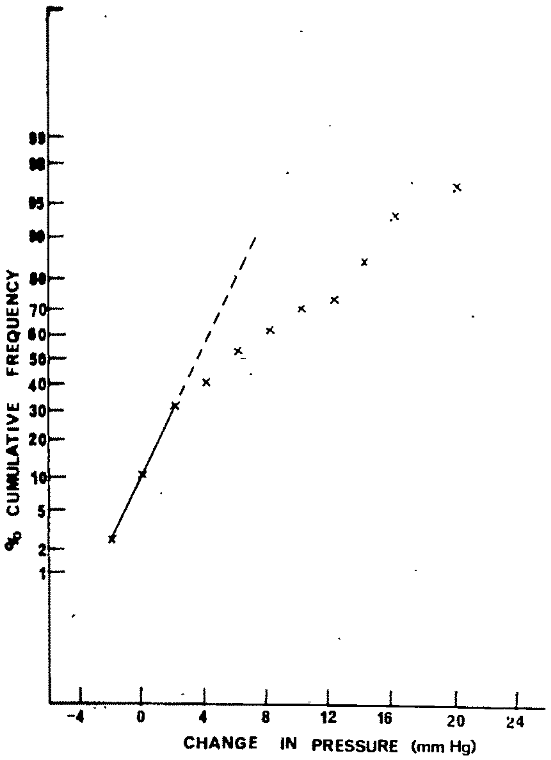

Fig. 6 *Percentage cumulative frequency distribution of corticosteroid-induced change in pressure in eyes with closed-angle glaucoma.*

patient might have on the corticosteroid-induced pressure response. The effects of other factors, such as patient motivation and compliance and time-delay effect on intraocular pressure, also become insignificant when the difference between the matched pair of eyes is considered. The logical deduction from this is that corticosteroid-induced ocular hypertension can be acquired by eyes that have sustained spontaneous episode of closed-angle glaucoma. Two possible explanations exist: (1) closed-angle glaucoma facilitates corticosteroid-induced ocular hypertension; (2) both closed-angle glaucoma and corticosteroid-induced ocular hypertension are due to a third common factor.

If one accepts that closed-angle glaucoma is a consequence of partial angle closure, then it is quite reasonable to suggest that partial angle closure could be the common factor to closed-angle glaucoma and corticosteroid-induced ocular hypertension. Partial-angle glaucoma is also a recognised mechanism in the pathogenesis of some primary open-angle glaucoma and ocular hypertension. Both these groups of patients have a higher prevalence of corticosteroid-induced ocular hypertenson than normal persons, and it seems logical to assume that the effect of the partial angle closure contributes to this higher prevalence.

Partial angle closure produces raised intraocular pressure, which inevitably leads to outflow damage. It would be interesting to identify which of the 3 factors, namely, partial angle closure, raised intraocular pressure, or damage to trabecular meshwork, is directly associated with corticosteroid-induced ocular hypertension. There is indeed no reason to presume that only one of these factors is involved; 2 or even all 3 could be.

There is evidence to suggest that the allele p^H either predisposes individuals to the development of corticosteroid-induced ocular hypertension or directly influences the magnitude of the pressure response of individuals to topical corticosteroids. If the possession of this gene is offered as being responsible for the 4 fellow eyes with positive corticosteroid pressure response (patient nos. 3, 18, 28, 34), then one would expect their corresponding closed-angle glaucoma eyes to have positive pressure responses. Not only do these 4 closed-angle glaucoma eyes have a positive corticosteroid pressure response

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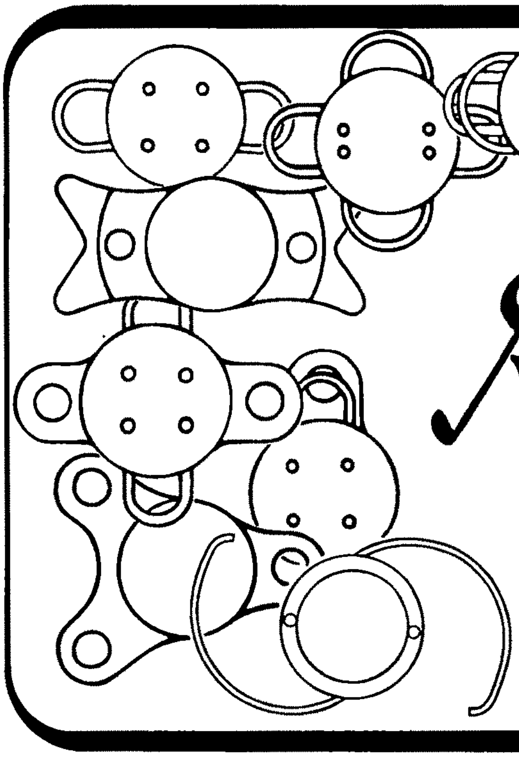

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but, as mentioned earlier, they show the highest change in pressure in the closed-angle glaucoma eyes. The implication of this is that the genetic influence and the effect of partial angle closure appear to be cumulative in the production of corticosteroid-induced ocular hypertension.

The interaction between genetic and acquired factors and other considerations make meaningless any sharp antithesis between genetically determined corticosteroid-induced ocular hypertension and that produced by acquired factors or environmental agents. There is in fact much overlap, and only in extreme cases can hereditary and acquired factors be clearly disentangled in the effect they produce.

In conclusion, corticosteroid-induced ocular hypertension does not appear to follow the simple Mendelian patterns of inheritance. It is suggested that the genetic factor in the aetiology is composed of one or more genes having a small, similar, or cumulative effect. The acquired factors acting on this genotype produce more of the phenotypic variations observed in the population than would be expected with a single gene trait. This pattern of inheritance has been termed multifactorial.

Clinical significance

The fact that corticosteroid-induced ocular hypertension can be acquired does not appear to be relevant to clinical practice at first. On further consideration the following points can be made:

1. A high corticosteroid pressure response is not a reliable indicator of future rising trend in intraocular pressure.

2. The role of the corticosteroid provocative test in the screening of individuals for glaucoma has to be revised.

3. Topical corticosteroids should be avoided in eyes with closed-angle glaucoma, especially during the postoperative period, when they are commonly prescribed. If there is an indication for their use, they should be restricted to one or 2 weeks, or the patient kept under closer observation. There is in fact evidence to suggest that the inflammatory activity in the anterior chamber after operation is not dramatically affected by topical corticosteroids (unpublished observation).

4. The fact that one eye in a patient does not respond to topical corticosteroid does not mean that the other eye will not respond.

I thank Mr R Mapstone for his inspiration and advice. I also thank the consultants who referred patients, Miss Sue Cowin for administrative assistance, Mr R. McBride for technical assistance, and Mrs M. D. Kelley for typing the paper.

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British Journal of Ophthalmology, 1982, **66**, 546

Correspondence

Incidence of optic disc haemorrhages in chronic simple glaucoma and ocular hypertension

SIR, How often do optic disc haemorrhages help us estimate the visual prognosis for patients with elevated intraocular pressure? If optic disc haemorrhages truly do precede retinal nerve fibre layer defects[1] and do signal increased risk of progression of visual field loss,[2 3] we as ophthalmologists need to know just how often we can expect to find this sign in our patients. In his article[4] Professor John Gloster is to be congratulated for the presentation of data from such a large number of photographs. There are, however, several serious problems with the article's methodology that limit application of its conclusions to all patients with elevated intraocular pressure.

Professor Gloster looked for optic disc haemorrhages in 1829 photographs of optic discs taken of 617 eyes of 320 patients with glaucomatous field defects and cupping, and of 284 eyes of 169 patients with at least one IOP measurement greater than 21 mmHg and who had no field defects, and he concluded that: (1) at least one-third of *eyes* (not *patients*, as the abstract states) affected by glaucoma show disc haemorrhages at some time or another; (2) 17% of glaucoma patients had disc haemorrhages; (3) there is a rising incidence of haemorrhage as the vertical cup:disc ratio increases; (4) there is a lower incidence of haemorrhages in ocular hypertension than in chronic simple glaucoma; and (5) more haemorrhages were found in eyes with lower IOPs than with higher IOPs.

As is common in such studies Professor Gloster's data are retrospective and not population-based, which, by his own admission, limits the accuracy and generalisability of his conclusions. He also did not have a control group. He simply looked at some of the disc photos of some of the people in the general ophthalmological population who had an intraocular pressure greater than 21 mmHg. It is not surprising that, as the number of photographs per patient increased, the incidence of disc haemorrhages per patient increased, because the decision to order disc photographs is inherently biased toward selecting those patients with positive or at least questionable findings by ophthalmoscopy. Professor Gloster states only that photographs were taken 'of a substantial proportion of the patients seen in the Glaucoma Unit,' a referral centre. He excluded an unspecified number of photos in which he was not sure that he could rule out small disc haemorrhages, again introducing a selection bias. Haemorrhages may be easier to rule in than rule out. Were the patients whose poor-quality photos were excluded different somehow from the rest of the glaucomatous population? One might hypothesise that, for example, chronic pilocarpine use might sometimes have inhibited pupillary dilatation and clear photography.

Neither the number of photographs taken of the patients' discs per examination, the interval between examinations, nor the number of follow-up visits per patient were standardised or controlled for. Moreover, the patients apparently were on various therapeutic regimens. It is quite possible that patients with poorly controlled IOPs, progressive field loss, previous haemorrhages, or greater cupping would have more frequent check-ups and more photographs taken. The total number of eyes with disc haemorrhage divided by the number of eyes photographed is 60/617, or 9·7%. Unless Professor Gloster is drawing his conclusions from the 10 eyes that were photographed 7 times each, how then can he make the statement, 'it is probable that at least one-third of affected eyes showed them [optic disc haemorrhages] at some time or another'?

As for relating maximum intraocular pressure recorded to the incidence of optic disc haemorrhage, in which he concluded that 'the incidence of haemorrhage was greater in eyes with lower intraocular pressures than in eyes with higher pressures,' he did not study the IOPs recorded at the time the photography was done but rather before therapy was begun, 'in some instances . . . several years before the photograph was taken.' It is well known that glaucoma patients can present at any stage in their disease, and that initial pressure does not correlate with field loss at 5-year follow-up. Patients vary considerably in their response to glaucoma therapy, which in Professor Gloster's article is not even specified, raising the question whether a lower incidence of haemorrhages is related to higher IOP or to some other factor correlated with initial (presenting) IOP.

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DAVID P. SUTTON

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SIR, Mr David P. Sutton has raised several points about the data presented and the conclusions drawn therefrom in my paper on 'Incidence of optic disc haemorrhages in chronic simple glaucoma and ocular hypertension.' He recognises that I made it clear that the study was retrospective and was not population-based. The limitations of such studies are well known, and include the possibility that unintended processes of selection make the results and conclusions unrepresentative of the clinical condition which we think we are studying. Mr Sutton cites several possibilities. He refers to an unspecified number of photographs which were excluded because I was not sure that I could 'rule out disc haemorrhages,' although the paper actually mentions the number of photographs in which a reasonably confident opinion could be given 'as to the presence or absence of a disc haemorrhage.' In other words, when a photograph was discarded it was because I had failed to make up my mind not only about the possible presence but also about the possible absence of a haemorrhage, and it is to be hoped that I succeeded in my attempt to give equal consideration to these 2 possibilities. Mr Sutton suggests that long-continued use of pilocarpine might have inhibited pupillary dilatation and clear photography, and this of course did sometimes happen. In some cases the problem was overcome by cessation of pilocarpine for a longer period before a subsequent attempt at photography, and I gained no impression of a grossly different photographic success rate in patients on miotics. On the other hand it is possible to argue that patients on nonmiotic therapy are more likely to be those who have lens opacities, and consequently they will be the ones less likely to give clear photographs. Some doubt must remain on this sort of problem, but whether such uncertainties can be completely avoided is another matter; for example, glaucoma patients with more than a certain degree of cataract will always be excluded from this sort of study, so some selection is inevitable. Mr Sutton is quite right in saying that such factors as the interval between photographs and the number of visits were not standardised. This was the point of my comment on p.455 that 'photography at regular intervals' should be aimed for in any future study.

With regard to the observed overall incidence of disc haemorrhages in glaucoma, it is to be expected that this will rise as the number of observations increases. Unfortunately, as was pointed out, the data were insufficient to allow accurate extrapolation to determine the incidence which could be expected with a very large number of observations on each patient. Nevertheless, consideration of the results of Table 1, for example by inspection of a simple graph, suggest that an overall incidence of around 30% is a reasonable minimum. It could easily be more. In this connection it is interesting that, in the study by Bengtsson *et al.*[1] to which Mr Sutton makes reference, somewhat similar results were presented as a graph of frequency versus number of observations, showing that 2/3 of glaucoma patients presented a disc haemorrhage within 4 visits, and it was stated that the hypothesis of disc haemorrhages occurring in all cases could not be rejected, although it was not proved. This effect of frequency of observation upon apparent incidence clearly has to be borne in mind when comparing groups of patients, and an attempt was made to do this. In Table 3, which related the incidence of haemorrhages to the cup:disc ratio, the average number of times eyes were photographed at various sizes of cup:disc ratio was given. This was also so for the relationship with level of intraocular pressure (Table 5). Mr Sutton says that I 'did not study the IOPs recorded at the time photography was done.' I did not really think that there was much point in doing this because of the varying preparation of patients for photography. Those on miotic therapy usually had their drops stopped, some for longer than others, those on nonmiotic therapy continued their treatment, some had acetazolamide for a day or two before photography, these variations being partly dependent upon previous response of the IOP to temporary cessation of treatment. In any case the level of IOP at photography probably bore no relationship to that at the time the haemorrhage occurred. The maximum IOP which had been recorded for each patient was chosen as the one by which cases could be divided into groups, because this method resembled the traditional division into 'low tension glaucoma' and 'chronic simple glaucoma,' but avoided the arbitrary choice of a dividing pressure level.

It does seem that the occurrence of disc haemorrhages in chronic simple glaucoma is worthy of more study. In particular one would like to know if haemorrhages really do occur at some time or another in all patients, whether they are part of the process leading to glaucomatous disc damage or merely one of the results thereof, and just what prognostic importance they have and so on. I hope that my paper indicated some of the advantages and disadvantages of basing investigations on photography, and I believe that it gave an idea of the scale of the investigation needed to get more accurate information than that which is available to us so far.

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Reference

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Herpes zoster ophthalmicus

SIR, In a recent article by Dr S. Lightman *et al.*[1] it was stated that as a result of a retrospective analysis of 1000 cases of herpes zoster ophthalmicus the great majority of the patients were 'healthy and therefore do not have diminished immunity.' The authors base these claims on the strength of a full blood count, differential white cell count and film, liver function tests, and electrophoresis, blood sugar, and chest *x*-ray. No attempt was made to assess quantitative immunoglobin levels, and T cell function was not assessed.

As the paper is entitled a 'Medical review' of herpes zoster ophthalmicus, why was an account of family history of compromised immunity or the patient's past immunisation history not documented? A physical examination was not mentioned.

This paper highlights the danger of reaching conclusions based on retrospective analysis.

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S. MURNAGHAN

Reference

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SIR, Active viral infection is associated with an alteration of T cell function, and assessment of T cell function in our patients on presentation with active herpes zoster would give no indication of the patient's basal immune status. The follow-up of our patients was for an average of 2 years, during which time no further infective episodes occurred, and therefore there was no medical indication for expensive immunological investigations. Family histories were taken from all patients and revealed no evidence of compromised immunity.

Since the most common age range of our patients was 50–70 years, immunisation histories are likely to be inaccurate, and most patients had difficulty recalling whether or not they had had chicken-pox.

These problems would be no different in a prospective study and do not detract from the conclusions reached in our paper.

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SUSAN LIGHTMAN
RONALD MARSH

Book reviews

Orbital Tumors. 2nd edn. By JOHN W. HENDERSON. Pp. 607. DM.194·00. Georg Thieme Verlag: Stuttgart. 1980.

The ophthalmologist is usually the first person to see patients with orbital disease, and his clinical horizon is thus opened to a wide variety of systemic, neurological, and developmental abnormalities which do not occur within the globe. The second edition of this work on orbital tumours appearing 8 years after the first edition is therefore to be welcomed. The distinguished author has collaborated with a pathologist, G. M. Farrow, also from the Mayo Clinic.

The strength of this book lies in the fact that the author has personally studied a series of 764 cases of orbital tumour and observed their natural history over many decades. This is an essentially personal book, which is embellished with good clinical photographs, supported by *x*-rays and numerous examples of pathological specimens. Presentation is excellent, and the bibliography is historically extensive, but many recent references of relevance seem to be omitted.

The material is considered in depth, with each condition receiving historical analysis, followed by aspects of clinical diagnosis and details of the pathological features. In any book covering so extensive a field there are omissions, but the failure to emphasise opticociliary shunt vessels as a characteristic feature of the nerve sheath meningioma is disappointing. Instead the authors describe papilloedema (presumably they mean disc oedema) and striae of the posterior wall of the eye (differential features of retinal and choroidal striae are now well established). There are many examples like this where clinical and descriptive terminological improvement is possible.

However, as the author indicates in the preface, the evolution of CT scanning has provided 'a wonderment beyond imagination' in orbital diagnosis. This wonderment is appropriate because only 8 of the 600 pages in this book are concerned with scanning. CT scanning is probably the most important diagnostic mode in orbital disease, and the absence of good examples of CT scans in the more common lesions is a major drawback to a book appearing in 1980.

This book is enjoyable to read and contains a great deal of information, but sadly a third edition encompassing the full impact of CT scanning will be necessary for the ophthalmologist of the 1980s.

M. D. SANDERS

Az Endogen Uveitisek És Általános Orvosi Vonatkozasaik. By LUGOSSY GYULA. Pp. 407. 116 Ft. Akadémiai Kiadó: Budapest, Hungary. 1980.

Dr Lugossy is well known to English ophthalmologists from his contributions to the meetings of the Ophthalmological Society of the United Kingdom. This monograph is the result of a lifelong study. The material consists of patients with uveitis observed and followed over 30 years in the Ophthalmic Department of the Rheumatology Institute in Budapest. His results are complemented by replies from questionnaires from hospitals in Hungary and other centres interested in the problem.

Chapters are devoted to epidemiology, classification, experimental uveitis, role of auto-antibodies, clinical and paraclinical investigations, and immunology. Two final chapters discuss the pathology of uveitis and the whole spectrum of aetiology. References at the end of each section are up to date and taken from English, French, German, and Russian literature.

Lugossy's writing is lucid and the presentation good. It is a pity that the print is on such glossy paper. For those who read Hungarian the book is inexpensive. At today's exchange rate it costs less than the price of a throw-away paperback and is strongly recommended to clinicians.

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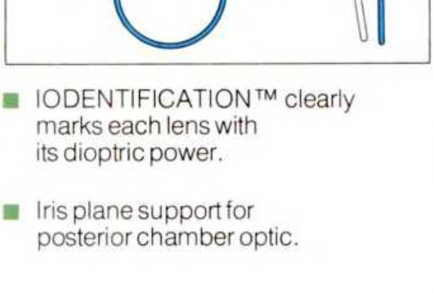

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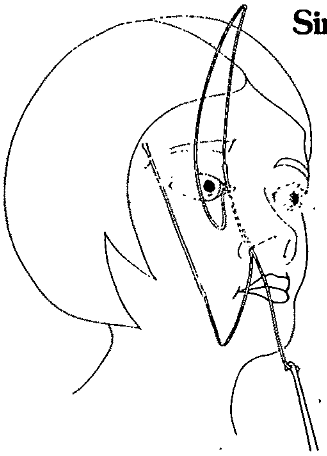

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Published by British Medical Association, Tavistock Square, London WC1H 9JR.
Typesetting by Bedford Typesetters Ltd., Bedford, England. Printed by Paramount Printing Co. Ltd., Hong Kong

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ASTM CODEN BJOPAL 66 (8) 477-548 (1982) ISSN 0007-1161

British Medical Association Tavistock Square London WC1H 9JR

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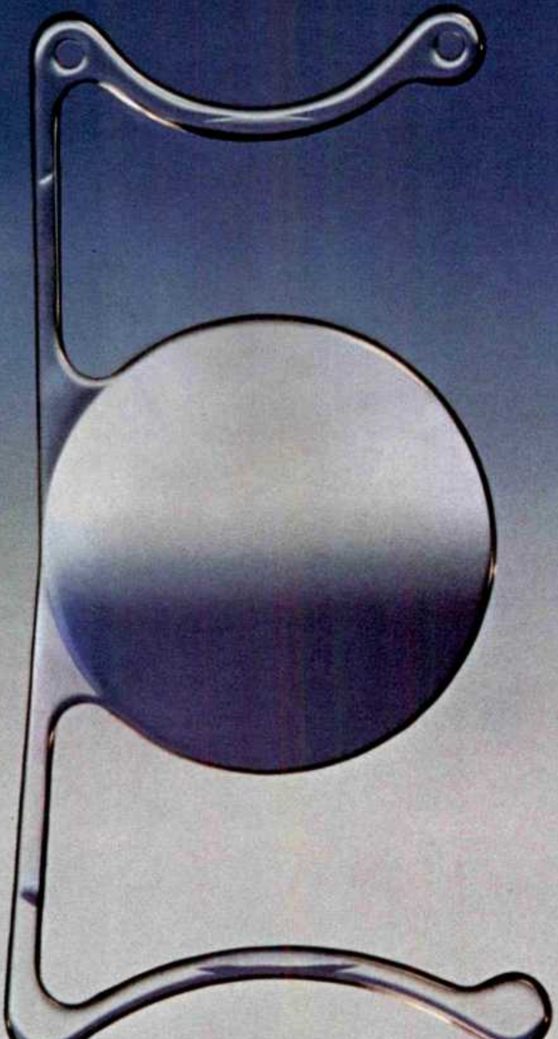

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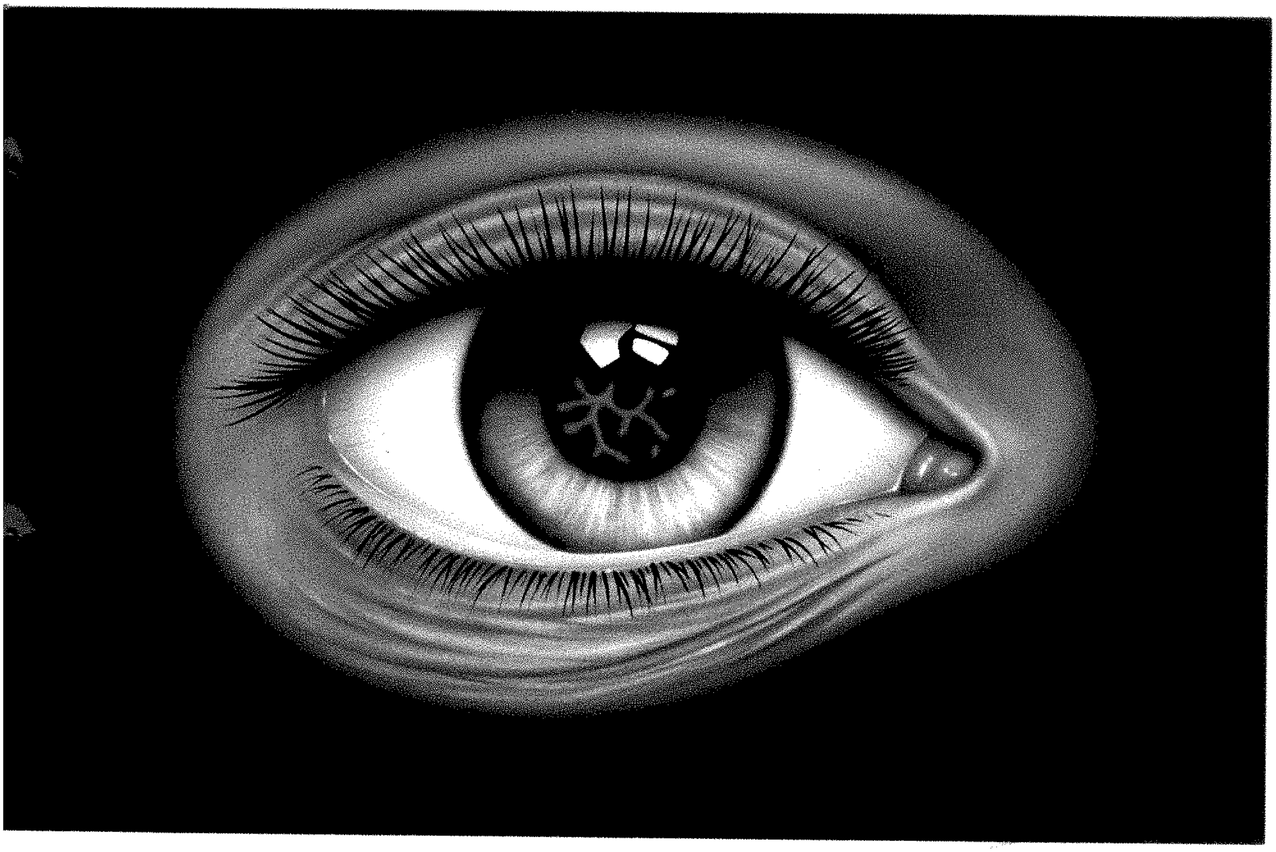

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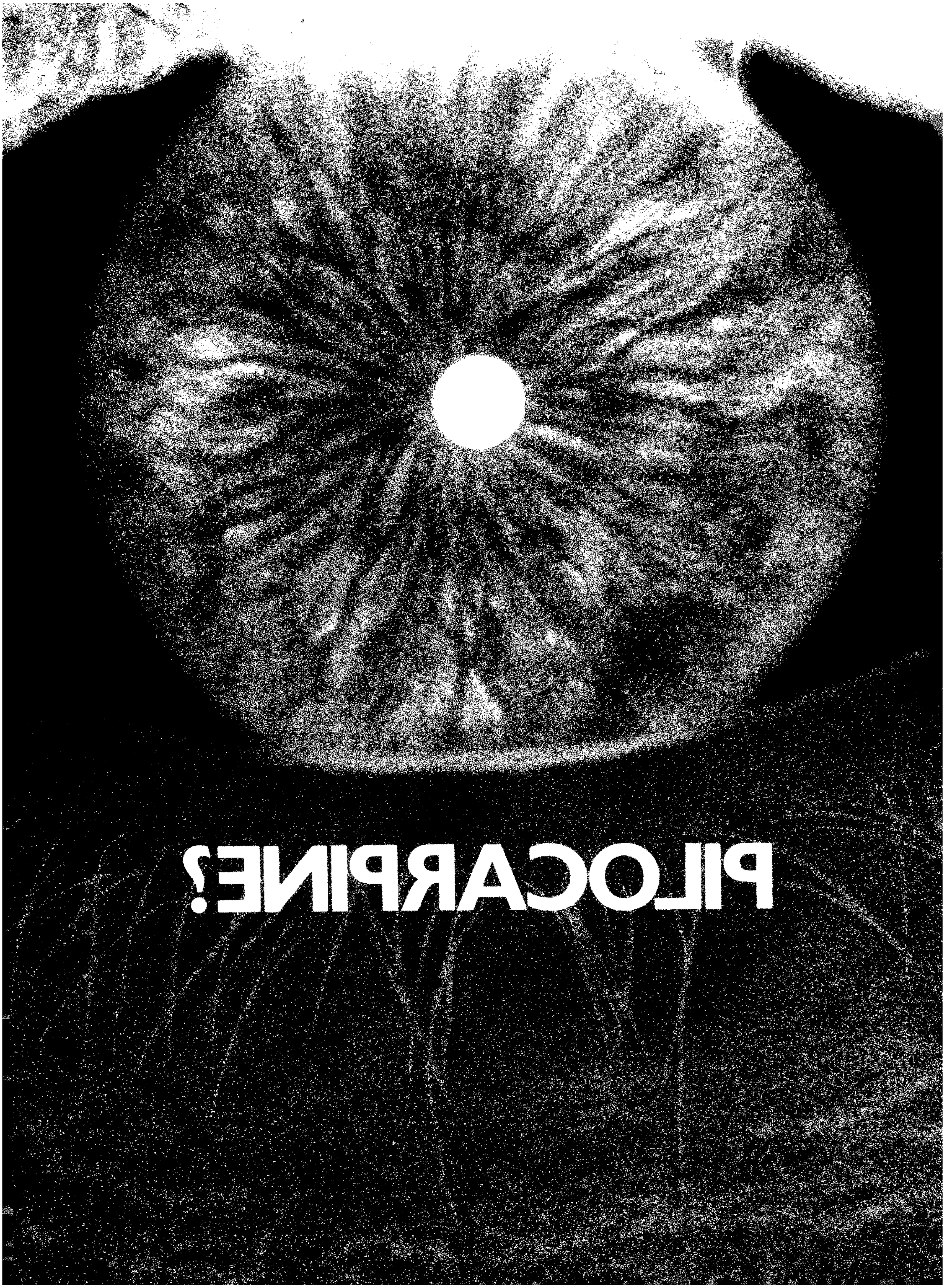
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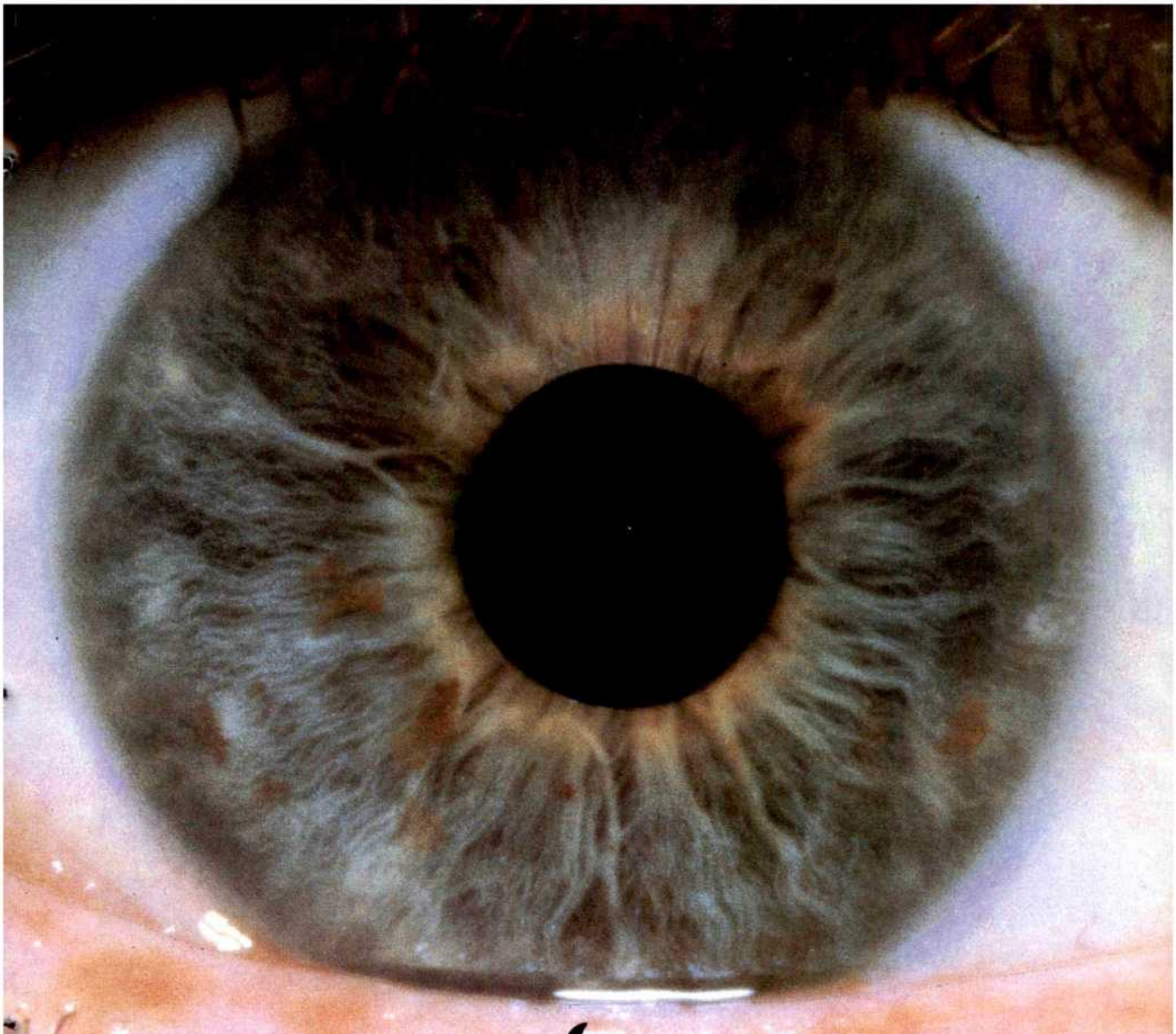

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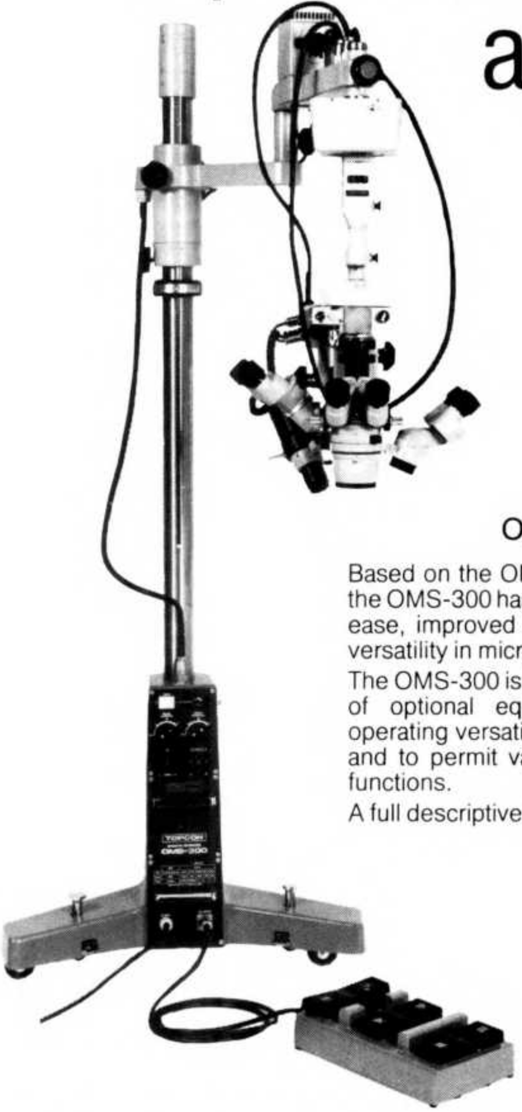

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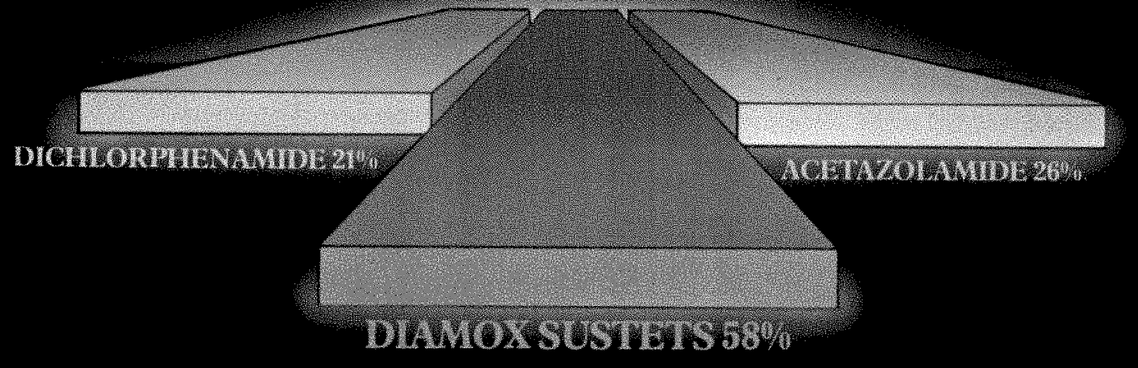

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British Journal of Ophthalmology, 1982, **66**, 549–555

Anterior segment consequences of blunt ocular injury

Y. M. CANAVAN AND D. B. ARCHER

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SUMMARY The anterior segments of 212 eyes (205 patients) were evaluated one to 14 years after contusional eye injuries. Anterior chamber angle recession was the commonest complication, occurring in 153 of 190 eyes examined (80·5%). However, only one patient developed ocular hypertension. Iris abnormalities were found in 37·3% of eyes injured, the most common abnormalities being marginal tears and pupillary defects. Cataract or lens dislocation attributable to trauma occurred in 24·5% of eyes, but most lens opacities were localised, stationary, and not associated with significant loss of vision. 15·4% of eyes developing lens opacities had cataract extraction within 18 months of the injury. Functional corneal sequelae were rare, but occasionally corneal opacities masked perforating injuries.

In most contusional injuries of the eye the anterior segment bears the brunt of both direct and indirect forces. The iris, filtration angle, lens, and zonule are particularly vulnerable, as they are poorly supported and have little resistance to acute stretching forces. Tissue repair of these specialised structures is very limited, nonspecific, and results in nonfunctional scars which remain as a permanent record of the original injury. Blunt injuries may also damage the posterior pole of the eye, although it is unusual to find significant lesions of the fundus in the absence of anterior segment lesions except in the uncommon situation where the force is applied directly to the sclera overlying the posterior segment.[1]

Most studies of ocular contusion relate to specific sequelae—for example, traumatic hyphaema,[2–10] anterior chamber angle recession,[11–24] concussional cataract,[25–26] lens dislocation,[27] blood staining of the cornea,[28] and corneal endothelial changes.[29] Few papers have reported the full spectrum of contusional anterior segment injuries in individual patients or assessed the relative susceptibility of the various tissues to damage. This report describes the different lesions of the anterior segment that follow severe blunt injuries to the eye, reports on their natural course, and discusses the various complications which may occur.

Materials and methods

A retrospective survey was undertaken of all patients with eye injuries requiring admission to the Ophthalmology Unit of the Royal Victoria Hospital, Belfast, during the 10-year period 1967–76 inclusive.[30] There were 1063 contusional eye injuries (49·2%) out of a total of 2162 injured eyes (2032 patients). One hundred and sixty-three patients (169 eyes) were available for review. A further 42 patients (43 eyes) who sustained contusional injuries during 1977–9 inclusive were also included. The following data is based on anterior segment evaluation of these 205 patients (212 eyes).

Most injuries followed sporting or domestic accidents (58·5%) and predominantly affected children (39·5%) (Table 1). Industrial accidents (9·8%) and assault (7·8%) accounted for a relatively small percentage of the total injuries. There were 175 males (85·4%) and 30 females (14·6%), and, of these, three-quarters (77·6%) were less than 30 years old

Table 1 *Distribution of cause of injury: 205 patients*

Cause of injury	*No. of patients injured*	%
Road traffic accident	13	6·3
Sport (adult)	33	16·1
Play and sport (children)	81	39·5
Civil disturbance	13	6·3
Industrial accident	20	9·8
Home accident	6	2·9
Farm accident	3	1·5
Assault	16	7·8
Unknown	20	9·8
Total	205	100·0

Correspondence to Professor D. B. Archer.

Table 2 *Final visual acuity: 212 eyes*

Final visual acuity	*No. of eyes injured*	*%*
6/6 or better	136	64·2
6/7·5–6/12	21	9·9 (including 3 amblyopic eyes)
6/18–6/36	13	6·1
6/60 or worse	27	12·7
No perception of light	13	6·1
Enucleation	0	0
Unknown	2	0·9
Total	212	99·9

Table 3 *Distribution of iris and pupillary injuries: 79 eyes*

	No. of eyes
Tears in pupil margin and pupillary abnormality	22
Tears in pupil margin	17
Traumatic mydriasis	4
Iridodialysis	8
Pigment clumps on anterior iris surface	5
Defects in pigment layer of iris	3
Sector iris atrophy	2
Multiple signs of iris or pupillary damage	18
Total	79

and nearly half (47·8%) were under 16. The commonest mode of presentation was hyphaema (81·1%). A final visual acuity of 6/6 or better was achieved in 136 eyes (64·2%). Twenty-seven eyes had a visual acuity of 6/60 or worse (12·7%), and in 13 eyes there was no perception of light due to extensive fundus injury or optic nerve damage (Table 2).

CORNEA

Twenty-five eyes showed evidence of corneal damage (11·8%). Superficial corneal opacities were found in 14 eyes, and of these 4 were vascularised. Five eyes had corneal opacities related to breaks in Descemet's membrane, and 4 eyes had dense endothelial pigment deposits. Two previously undetected full-thickness corneal scars were identified, and one patient had persistent corneal oedema and band-shaped keratopathy in a blind disorganised eye. Eleven patients had total hyphaemata; 4 of these had raised intraocular pressure and 5 required anterior chamber irrigation. None of these patients showed any evidence of corneal blood staining.

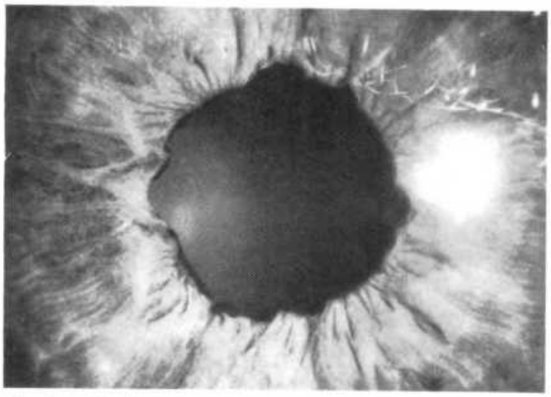

Fig. 1 *Iris photograph showing multiple notches of the pupillary margin.*

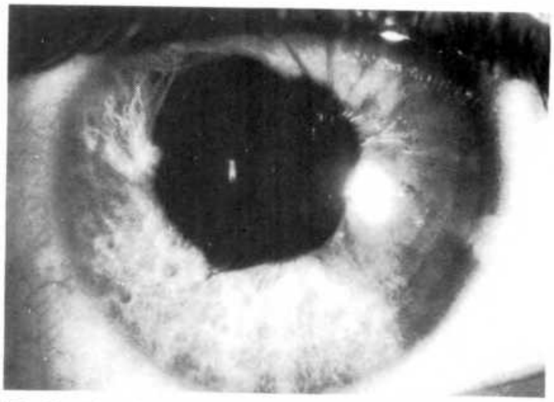

Fig. 2 *Anterior segment photograph showing radial full-thickness iris tear and 2 pupillary notches.*

IRIS AND PUPIL

Seventy-nine (37·3%) eyes had iris or pupillary abnormalities (Table 3). Tears of the pupillary margin were most common and characteristically involved the sphincter muscle, producing a focal or sectorial defect. Small sphincter tears characteristically produced notches in the pupillary margin (Fig. 1), while in more severe injuries multiple tears

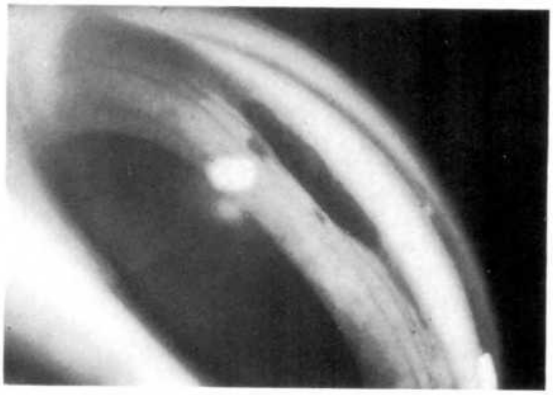

Fig. 3 *Goniophotograph showing small occult iridodialysis.*

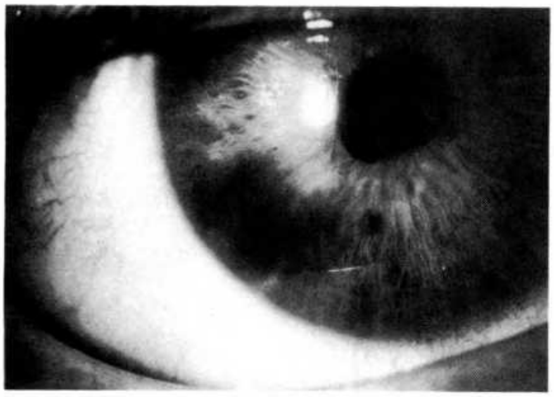

Fig. 4 *Photograph of right iris demonstrating circumscribed area of pigment deposition over surface of inferotemporal iris.*

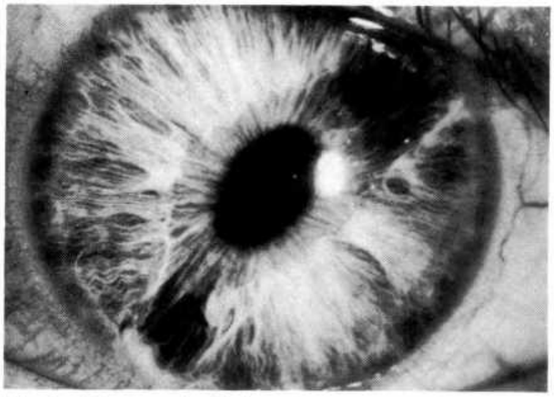

Fig. 5 *Photograph of left iris showing 2 areas of stromal atrophy and associated pupillary abnormality.*

involved up to three-quarters of the pupillary margin with severe compromise of pupillary function. Occasionally radially disposed tears extended from the pupil margin to the peripheral iris (Fig. 2). Permanent traumatic mydriasis occurred in 4 eyes, the pupils bring unreactive to direct and consensual stimulation. Eight eyes had iridodialyses, which varied from small defects visible only on gonioscopy (Fig. 3) to larger defects involving up to 120° of the peripheral iris. One eye had a radial tear of the peripheral iris adjacent to a full-thickness corneal scar suggesting an occult perforating injury. Defects in the pigment layer of the iris were common and in 3 instances were extensive. Five eyes had focal or diffuse clumps of pigment adherent to and distributed over the anterior surface of the inferior iris (Fig. 4). Patchy atrophy of the iris stroma was common, at times involving its full thickness (Fig. 5). Forty-four (55·7%) of 79 eyes with iris or pupillary abnormalities had juxtaposed, localised lens opacities.

ANTERIOR CHAMBER ANGLE

Gonioscopy was undertaken in 190 eyes but not attempted in 22 young children. One hundred and fifty-three eyes (80·5%) had evidence of angle recession. The degree of angle recession was graded by the classification recommended by Howard *et al.*[15] and Mooney.[20]

Grade I (shallow angle tears). No discernible cleft visible in the face of the ciliary muscle, but the ciliary body band appears darker and wider and the scleral spur whiter than in the fellow eye owing to tearing of the uveal meshwork.

Grade II (moderate angle tears). The angle is deeper than that of the fellow eye owing to a tear into the face of the ciliary body (Fig. 6).

Grade III (deep angle tears). A deep fissure extends into the ciliary body. The apex of the fissure cannot be identified gonioscopically.

A further category, *Grade IV*, was introduced to describe one patient who had a subtotal detachment of the ciliary body (Fig. 7).

Other angle abnormalities which occurred with or without angle recession included dense pigment deposition, peripheral anterior synechiae, and proliferation of fibrous tissue at the root of the iris.

The 190 eyes examined were grouped according to the severity of angle changes (Table 4). Of 153 patients whose eyes showed angle recession only one had a rise of intraocular pressure in the injured eye (35 mmHg). In this instance there was grade II recession involving 360° of the angle. In addition the lens was subluxated, and an inferotemporal retinoschisis was present. Despite moderate

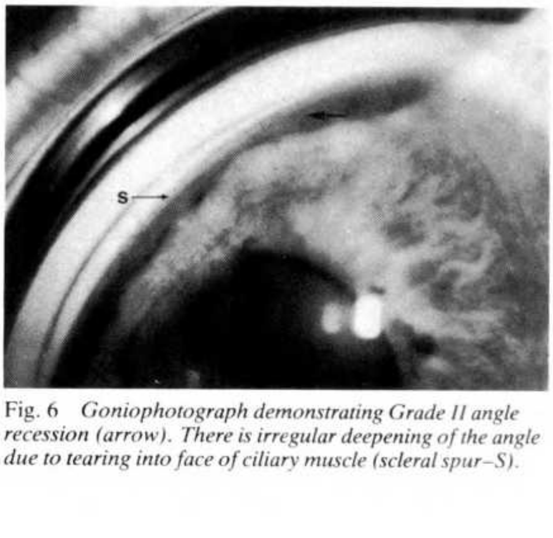

Fig. 6 *Goniophotograph demonstrating Grade II angle recession (arrow). There is irregular deepening of the angle due to tearing into face of ciliary muscle (scleral spur–S).*

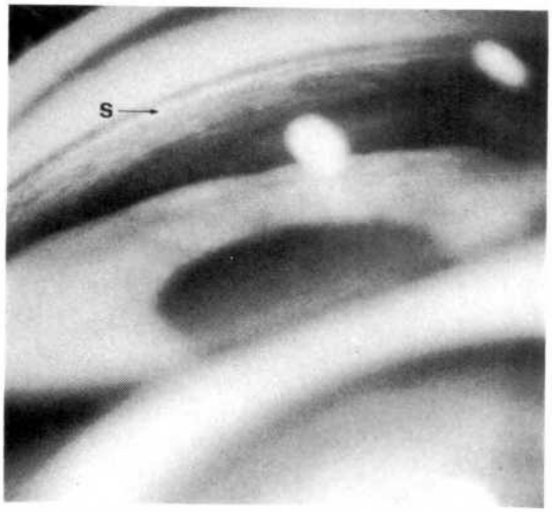

Fig. 7 *Goniophotograph demonstrating deep angle tear with extensive detachment of the ciliary body (scleral spur–S).*

elevation of intraocular pressure there were no signs of glaucomatous optic atrophy or visual field defects beyond peripheral constriction corresponding to the site of retinoschisis.

LENS

Lens opacity or dislocation was present in 59 eyes.

Table 4 *Grading of angle recession: 153 eyes*

Group		*No. of eyes*
A	No angle recession	37
B	Insignificant patchy grade I angle recession (less than 180°)	53
C	Significant grade I angle recession (more than 180°) plus small patches of grade II recession	35
D	Significant grade II angle recession (more than 180°) plus small patches of grade III recession	32
E	Peripheral anterior synechiae plus various grades of angle recession (more than 180° of angle involved)	33
Total		190

Table 5 *Distribution of lens injury: 52 eyes*

Group		*No. of eyes*
1	Lens opacities without dislocation	29
2	Lens opacities with dislocation	15
3	Aphakia following surgery for traumatic cataract	8
Total		52

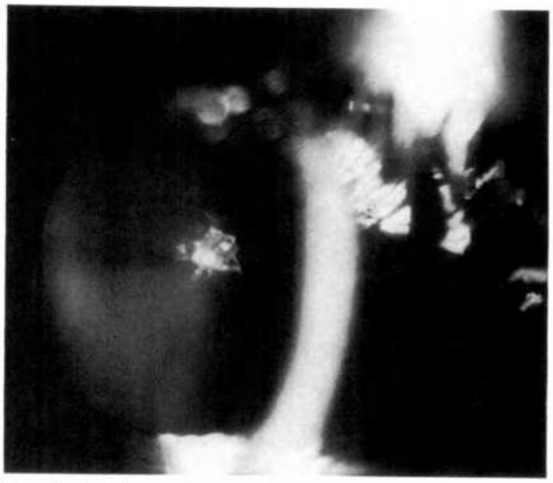

Fig. 8 *Slit-lamp photograph showing a circumscribed anterior subcapsular lens opacity.*

Three eyes had bilateral symmetrical lens changes which were judged to be either congenital or senile. Three patients had phthisical eyes with cataract and one patient had iridodonesis in the presence of a clear lens. These patients were not considered further. The 52 eyes (24·5%) with unilateral cataract attributable to contusion were divided into 3 groups (Table 5).

Group 1. Lens opacities without dislocation (29 eyes). Ten eyes had localised anterior cortical lens opacities (Fig. 8) and 6 had localised posterior cortical lens opacities. Nine eyes had a combination of anterior and posterior cortical lens opacities and one eye had a mature cataract. Three eyes had raised central anterior capsular scars consistent with healed capsular ruptures (Fig. 9) and were associated with

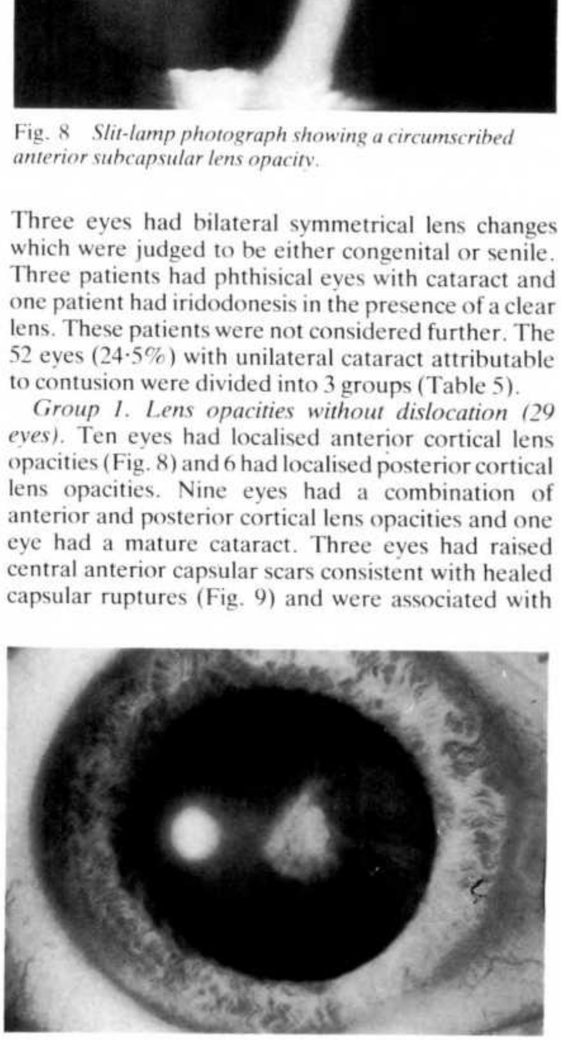

Fig. 9 *Anterior segment photograph showing a localised anterior capsular/subcapsular lens opacity with radially disposed striae probably representing a healed capsular rupture.*

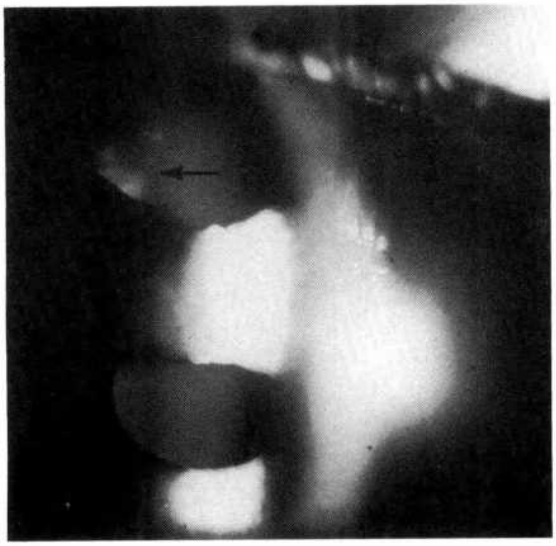

Fig. 10 *Slit-lamp photograph illustrating a superiorly situated iridodialysis through which a localised lens opacity is visible (arrow).*

anterior and posterior cortical opacities. Most lens opacities were punctate or 'cobweb' in nature, and in only 3 instances were typical rosettes present. Focal lens opacities secondary to posterior synechiae and acute ocular hypertension (glaucomflecken) were occasionally noted.

Group 2. Lens opacities with dislocation (15 eyes). Patients in this group had a wide range of lens alterations. Advanced cataract was present in 2 eyes and there were combined anterior and posterior cortical lens opacities in 5 eyes. Anterior cortical opacities were present in 3 eyes, posterior cortical opacities in 2, lamellar cataract in one, and a further patient had a localised peripheral lens opacity observed through an iridodialysis (Fig. 10). One patient had a dislocated cataractous lens suspended in the inferior vitreous.

Lens opacities in groups 1 and 2 remained stationary over the years of follow-up in all but one case.

Group 3. Aphakic eyes following surgery for traumatic cataract (8 eyes). Eight patients required cataract extraction, discission, or lens washout. The need for operation became evident within 18 months of injury.

Traumatic iris lesions were present in 50 of 52 eyes with cataract. There was a close anatomical relationship between the site of iris damage and the location of the lens opacity in most cases. Gonioscopy was possible in 46 of 52 patients with cataract, and angle recession was noted in 44 instances.

Discussion

The precise mechanism of intraocular damage following contusional injury to the eye is not understood, though according to Duke-Elder[31] most damage can be attributed to an equatorial distension of the globe following anteroposterior compression. Localised injury may occur at the point of impact, though most severe contusions inflict damage elsewhere secondary to shock waves traversing the interior of the globe—that is, contrecoup injury. Wolter[32] adapting Courville's[33] mechanism of brain contrecoup injury concluded that a similar injury of the eye could be explained by a line of force traversing the eye, causing damage at all interfaces. The multiplicity of sites of anterior segment damage following blunt injury is explained in part by the dynamic effects of a wave of aqueous forcing the iris backwards against the relatively unyielding lens, which in turn rebounds from the vitreous face. It is also believed that aqueous is forced laterally, impinging on the relatively unsupported iris diaphragm and angle of the anterior chamber. Dilatation of the corneoscleral ring compensates for the anteroposterior compression of the globe and is counteracted by an immediate contraction of the sphincter of the iris, which may be followed by mydriasis secondary to sphincter damage.

Corneal and conjunctival damage may follow either focal or generalised concussional injury. Most lesions, such as subconjunctival haemorrhage, conjunctival oedema, or corneal epithelial abrasions, resolve without sequelae. More prolonged corneal oedema may result from endothelial disturbances, and associated breaks in Descemet's membrane may lead to permanent scars. In general the corneal endothelium is resistant to contusional damage and recovers function rapidly despite the presence of intracameral blood, raised intraocular pressure, endothelial deposits, breaks in Descemet's membrane, or decrease in endothelial cell density.[29] Few corneal opacities require treatment, and in none of the injuries in this series was corneal surgery or contact lens fitting required. Full-thickness corneal scars may obscure a perforating injury, and such patients should have a full anterior segment evaluation with this in mind and x-ray of the globe to exclude a retained intraocular foreign body.

The iris, because of its mobility, lack of support, and thinness, is particularly susceptible and sensitive to blunt trauma. Iris lesions characteristically fail to heal and remain a hallmark of previous ocular trauma. The pupillary margin of the iris appears to be the most susceptible region to trauma, and small iris notches are observable in most patients who have had a significant contusional injury. The iris sphincter and stroma are also vulnerable, and full-thickness tears lead to functional abnormalities of the pupil. Damage to the pigment layer of the iris characteristically occurs at the root of the iris, and such lesions are best identified by retroillumination. Iridodialyses are relatively infrequent and vary from small tears identifiable on gonioscopy to complete avulsion of the iris diaphragm. Although traumatic mydriasis is a frequent finding in the acute stage of injury, a permanent, significant mydriasis is uncommon.

The incidence of angle recession in this series (80·5%) agrees closely with that found by Blanton,[14] who noted a 71% incidence of angle recession in a series of 182 eyes. The reported incidence of angle recession following ocular contusion complicated by hyphaema varies from 20%[15] to 94%.[16] Angle recession becomes more difficult to identify with the passage of time, and Herschler[23] states that the appearance of the recessed angle changes dramatically during and after the first week of injury. The incidence of peripheral anterior synechiae in the present series is high, and it is likely that these synechiae may mask areas of angle which were previously recessed. Despite the common occurrence of angle recession in ocular contusion the association of ocular hypertension or glaucoma was not a feature in this series. Several workers[13 21 22] have suggested that, if more than 180° or 240° of the angle is involved, glaucoma may occur and follow-up is indicated. In this survey only one patient with angle recession had a raised intraocular pressure, and in this case other factors were present which may have contributed to the high pressure. Longer follow-up may identify additional cases of ocular hypertension or glaucoma, but the overall impression is that glaucoma is a relatively rare accompaniment of angle recession.

In this study the majority of contusional cataracts remained localised to the anterior and posterior subcapsular and cortical regions and were typically non-progressive. Those eyes which showed progressive lens changes usually required surgery within 18 months of injury. These findings are similar to those of Roper-Hall[25] and Davidson,[26] who emphasised that the prognosis should be more guarded in the older age groups, where senile lens changes may be intensified and accelerated. The coexistence of iris tears or angle recession in these patients is useful evidence that trauma may have contributed to cataract formation. Partial dislocation of the lens is a frequent complication of blunt trauma, resulting in iridodonesis and eccentric deepening of the anterior chamber. Prolapse of vitreous into the anterior chamber was not a feature of our series. There is often a precise anatomical relationship between lens opacities and iris lesions.

Most eyes recover and retain good visual functions after contusional injury confined to the anterior segment despite frequent widespread structural changes. About two-thirds of our patients regained a visual acuity of 6/6 or better. This is in contrast to blunt injury involving the posterior segment, in which the visual prognosis is less favourable.

We are grateful to the Eastern Health and Social Services Board for providing a research grant from the Endowment Fund of the Royal Victoria Hospital to facilitate this project.

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British Journal of Ophthalmology, 1982, **66**, 556–559

Control of astigmatism after surgery and trauma

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SUMMARY Since the introduction of microsurgical accuracy in the closure of corneal wounds, there have been fewer complications due to imperfect wound closure. As a result the eye is much safer after intraocular surgery or trauma. There may, however, be an undesirable and irregular refractive error. Much thought has been given to the prevention of this by attention to other details during closure of wounds. Interest has been revived in surgery for the correction of inherent refractive errors. The methods used for such conditions may also be applied to residual distortion after surgery or trauma. The possibility of adjustment during the early postoperative period has escaped detailed consideration. This neglected approach to the control of astigmatism is discussed in this paper.

Most postoperative astigmatism is due to inaccurate wound closure. Attempts have recently been made[1–5] to prevent this by detailed attention to surgical technique assisted by operating keratometers. When this is unsuccessful, a secondary corrective procedure involving resection, grafting, or keratotomy can be applied. Despite these efforts some patients end up with a gross astigmatism in an otherwise good eye. It is sometimes suggested that such astigmatism can be reduced by suture removal, but this is not very predictable and sometimes it can be made worse.

Adjustment of a continuous suture or removal of one or more selected interrupted sutures during the early postoperative weeks can allow a refined control. This possibility has been given scant attention but has a number of advantages. It can be applied at the time of postoperative consultation and refraction assessment. The effect is often dramatic and immediate and is subject to less subsequent alteration than secondary operative procedures. It can be applied to corneal distortion following trauma as well as cataract extraction and keratoplasty. It sets aside some of the difficulties in predicting the final refractive error at the time of primary surgery.

Surgically induced astigmatism

The pattern of surgically induced astigmatism was well known at the end of the last century and several authors studied ways of controlling it.[6 7]

Wound slide in a classical cataract section usually causes a fairly regular astigmatism 'against the rule.' The nearer the wound to the centre of the cornea, the greater the astigmatism. It follows that traumatic lacerations near the corneal periphery usually cause regular astigmatism, with flattening of the meridian at right angles to the scar. This is equivalent to a convex (+) cylinder with its axis parallel to the wound. If the damage extends to involve the central cornea, there is irregular and often gross astigmatism.

Wound closure has become much more secure and accurate since the advent of microsurgery. This has greatly reduced the incidence of postoperative complications such as hyphaema, iris prolapse, wound leakage, and shallow anterior chamber, which are related to defective wound healing. However, firm wound closure can induce astigmatism, and in cataract surgery, contrary to previous experience, this is usually 'with the rule.'

Many papers have been published on this surgically induced astigmatism and how to control it.[1–5] Most of them consider ways in which it can be prevented by surgical technique and by intraoperative keratometry.

Careful realignment and apposition of the wound while suturing can make it watertight without being overtightened. During closure judgment is assisted by the presence of an air bubble in the anterior chamber, which highlights stress lines in the cornea if the suture is too tight or the wound misaligned.

In recent years various forms of keratometer have been designed for use with the operating microscope in the hope of obtaining the desired firmness and regularity of wound closure so that an ideal postoperative refraction results. There are difficulties in achieving this. Accuracy is limited with simple

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keratometers, which utilise an illuminated ring reflecting a circle of light from the corneal surface, and up to 3 dioptres of astigmatism may be present even when the reflection appears to indicate a spherical form. This is little or no better than surgical control under the microscope alone.

More accurate keratometers can be used during planned surgery,[8] but even if the desired corneal curvature is obtained at the end of operation the final postoperative refraction is still not fully predictable. Conditions at the end of surgery are abnormal, healing processes are subject to many variables, and these often lead to changing refraction.

At the end of operation the eye will usually be hypotensive, and this could affect the measurements. The ultimate refraction will depend upon the healing process in the tissues and may not be equally rapid in all parts. This will be affected by factors individual to the patient. The way in which the tissues react to the suture material is also variable, and some sutures may cut tissue by a necrotic process due to overtightness. The final astigmatism will be influenced too by the extent of the incision; even a small wound may have much astigmatism, and some extensive wounds can show little cylinder due to neutralisation of astigmatic forces.

Since the final refractive error after full-thickness corneal incision is subject to so many variables, a keratometer may not prove to be so practical a clinical tool as it may seem.

Refractive surgery

Attempts have been made in the past to control refractive errors by corneal sculpturing (keratomileusis) or relaxing incision (keratotomy),[6 9–11] and the latter has been given renewed attention more recently.[12 13] Public interest has been aroused by the suggestion that radial keratotomy can correct errors which would otherwise require the lifetime wearing of spectacles. It has attracted patients with relatively low myopia, and many have submitted themselves to surgery, with as yet uncertain end results.

Although the effect of nonperforating wounds on astigmatism was studied by Lans in 1898,[6] it was Sato whose name is most usually associated with early attempts at refractive surgery.[10 11] He wrote with great enthusiasm of his methods and their results, claiming that the operation was indicated for all cases of astigmatism over 2 dioptres. Serious complications were encountered, and after a few years the procedure was generally condemned.

After his experience of using radial keratotomy, with which he claims to have had no complications over a period of 5 years, Fyodorov[12] has during the past 4 years studied the effect of applying anterior keratotomy incisions to the correction of astigmatism. He reports excellent results in 126 eyes of 76 patients and describes different patterns of incision for different degrees of astigmatism. Most of these are related to errors up to 4 dioptres. In the experience of other surgeons the method does not seem to be free of complication, and some reports of adverse effects of the more recent operations are now being made.[13]

It may be more difficult, as Fyodorov states, to treat high refractive errors, but there is a greater need to apply our efforts to the control of irregular astigmatism which cannot be corrected by spectacles or contact lenses than the refractive errors for which these optical appliances can so easily be used.

The methods introduced for the surgical reduction of refractive errors can also be applied to the correction of surgically or traumatically induced errors, but it is undesirable that a second operative procedure should be required for correction of such errors after planned surgery.

Adjustment of astigmatism in the postoperative phase

A cornea with a large incision can show quite substantial alterations of refraction during the first 8 postoperative weeks. Thereafter it becomes more stable, and after a year little alteration is seen.

It is unsafe to remove all corneal sutures at an early stage, and, although it has been stated that their removal will reduce astigmatism, this is by no means consistent (Table 1). However, since the cornea is subject to variation during the early weeks of healing, there is an opportunity of adjusting an astigmatic refraction. This possibility has escaped detailed consideration, but very effective adjustments can be made, and these may control larger errors than are amenable to refractive surgery.

Method

Selected suture removal is applied to wounds closed by interrupted sutures. Continuous sutures can be adjusted without removal. Both these actions can be undertaken at the slit-lamp with topical anaesthesia.

INTERRUPTED SUTURES

Provided sutures have been placed at intervals no greater than 1·5 mm apart it is possible to remove

Table 1 *Comparison of astigmatism at 6 months with that after 2 years: 283 corneal wounds*

Power unchanged	109
Less astigmatism	120
More astigmatism	54

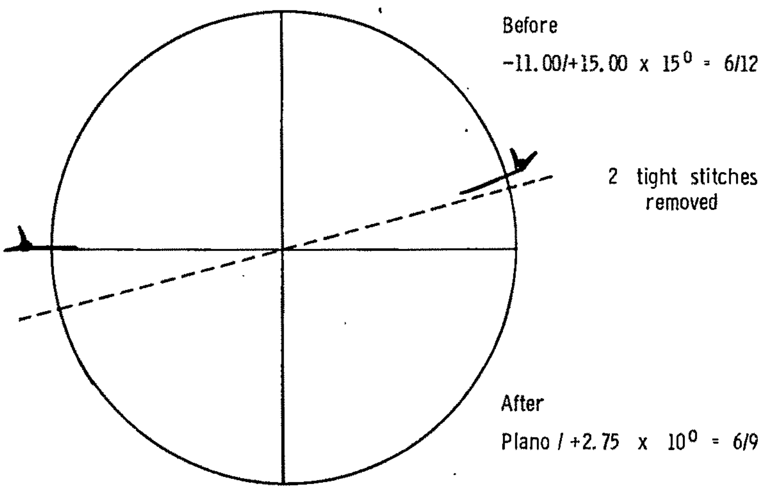

Fig. 1 *Selected suture removal.*

individual sutures without threatening wound security.

Usually a tight suture will be found on the axis of the + cylinder, and, if this is removed, there is an immediate reduction of astigmatism. The refraction can then be reassessed and the process repeated until the optimal correction is obtained.

CONTINUOUS SUTURES

It is possible to adjust the tension of a continuous suture by sliding it along the wound.

The power and axis of astigmatism is established. Microsurgical suture forceps can then be used to grip the continuous polyester suture through the corneal epithelium and ease it towards the tight meridian (the

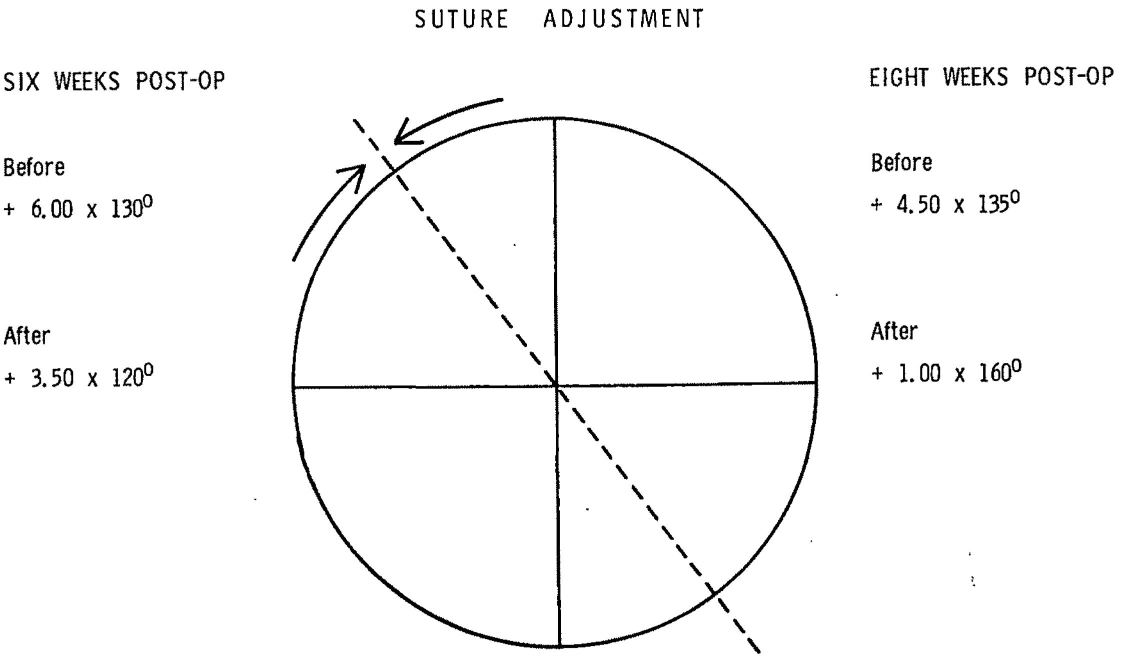

Fig. 2 *Suture adjustment.*

+ axis). The change of refraction is usually immediate, and after reassessment the adjustment can be repeated if necessary.

Case reports

A large series of cases is being analysed to quantify the method, but 2 examples will illustrate the potential of the 2 methods.

SELECTED SUTURE REMOVAL (Fig. 1)

Case 1. Manager aged 52 years. Old herpes simplex.

11 Jan 1981. Right *penetrating keratoplasty* 7·5 mm into 7 mm; 8 interrupted and 1 continuous 10/0 nylon suture.

12 Mar 1981. −11·00/+15·00 axis 15°=6/12+.

18 Jun 1981. No change in refraction. Tight 10/0 sutures removed at 2.30 and 9 o'clock. Immediate change of refraction to +2·75 axis 10°=6/9.

Comment. Immediate reduction of 12 dioptres of astigmatism when selected sutures removed 5 months after operation.

In keratoplasty, owing to the more central incision and slower healing, the adjustment can be made later in the postoperative period than is the case with incisions near the corneal periphery.

SUTURE ADJUSTMENT (Fig. 2)

Case 2. Retired administrator aged 60 years. Cataract.

26 Sep 1980. Right cataract extraction. Interrupted 8/0 silk suture at 12 o'clock and continuous 10/0 nylon from 9 to 3 o'clock with anchoring loops at each end.

6 Nov 1980. +6·00 axis 130°. 10/0 suture eased to 10 o'clock. Immediate change of refraction to +3·50 axis 120°.

20 Nov 1980. +4·50 axis 135°. Suture eased to 10.30 o'clock. Immediate change of refraction to +1·00 axis 160°.

29 Oct 1981. 6/5 unaided. 10/0 suture intact.

Comment. Immediate reduction of astigmatism when suture eased towards the tight meridian 6 and 8 weeks after surgery. This reduction of 5 dioptres has been maintained.

Conclusion

There are a number of ways in which corneal astigmatism can be prevented or treated. As soon as accurate refraction is possible, the early postoperative period of wound healing allows accurate adjustment with the convenience of simplicity.

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British Journal of Ophthalmology, 1982, **66**, 560–566

Vitreous fluorophotometry in optic nerve disease

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SUMMARY Posterior vitreous fluorophotometry measurements have been shown to be increased in patients with acute retrobulbar neuritis. We studied 12 patients who had optic neuropathy by posterior vitreous fluorophotometry, with and without correction for blood fluorescein concentration. Both uncorrected and corrected posterior vitreous measurements were increased in patients with inflammatory, obstructive, and infiltrative optic neuropathies. Concurrent values from anterior chamber fluorophotometry were not increased in any of the 8 patients studied.

Inflammation of the optic nerve head includes both clinically visible and inapparent abnormality of the optic nerve. We refer here to optic neuritis as apparent optic nerve head inflammation indicated by clinical and/or fluorescein angiographic abnormality. Retrobulbar neuritis is defined as optic nerve head inflammation not detectable by ophthalmoscopic or fluorescein angiographic abnormality.

It has been shown that posterior vitreous fluorophotometry readings increase in acute attacks of retrobulbar neuritis and return to normal levels on resolution.[1] Recurrences of retrobulbar neuritis also give increased readings on posterior vitreous fluorophotometry.[1] The purpose of the present study was to investigate optic neuropathies by vitreous fluorophotometry, and we emphasise the value of this technique when fluorescein angiography gives normal results. Recent modifications have been made in the interpretation of vitreous fluorophotometry readings, by the use of blood fluorescein concentrations.[2] These were used in the majority of patients studied. We also investigated the value of concurrent fluorophotometric readings in the anterior chamber.

Materials and methods

Twelve patients with optic nerve disease from the Ophthalmology and Neurology Departments of the University of Illinois and West Side Veterans Administration Hospitals were examined. Both eyes of all patients were examined. Three patients had retrobulbar neuropathy: cases 1 and 2 had unilateral idiopathic retrobulbar neuritis, and case 3 had ethambutol/isoniazid (toxic) retrobulbar neuropathy (Table 1). Four patients had optic atrophy in one eye: case 4 had multiple sclerosis, cases 5 and 6 had recurrent idiopathic optic neuritis, and case 7 had systemic lupus erythematosus and optic neuritis (Table 1). Cases 4 and 5 had optic neuritis superimposed on optic atrophy. Five patients had clinical and/or angiographic evidence of disc oedema and/or hyperaemia: case 8 had bilateral idiopathic optic neuritis, cases 9 and 10 had unilateral idiopathic optic neuritis, case 11 had unilateral (presumed sarcoid) optic neuritis, and case 12 had bilateral papilloedema secondary to obstructive hydrocephalus (Table 2).

All 12 had a complete eye examination, which included best corrected distance and near vision (at 14 inches (36 cm) with a Lebensohn chart). The neuro-ophthalmological examination included pupil assessment (particularly to detect an afferent pupillary defect), motility, nystagmus, colour vision comparison between the eyes (red and green bottle tops and/or Hardy-Rand-Rittler plates), black-and-white Amsler grid, and Goldmann visual fields of both eyes. Slit-lamp biomicroscopy, applanation tonometry, and dilated fundus examination with scleral depression were performed on all patients. Optic nerve assessment was done by at least 2 observers. Fundus photography, fluorescein angiography, and vitreous fluorophotometry were performed on all the patients at least once.

An injection of 25% sodium fluorescein was given in a dose of 14 mg/kg of body weight. Fluorescein angiography was performed on the affected eye (or

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Table 1 *Patients with retrobulbar neuritis (cases 1-3) and optic neuritis with optic nerve head pallor (cases 4-7)**

Case no. sex, age (yr)	*Days between visual loss and testing*	*Sympto-matic eye*	*Best corrected visual acuity*				*Disc oedema and/or hyperaemia*		*Fluorescein angiography: late disc staining and/or leakage*		*Posterior vitreous fluorophotometry*					*Remarks*
			Distance		*Near*						*Uncorrected†*		*Bld‡*	*Corrected†*		
			OD	*OS*	*OD*	*OS*	*OD*	*OS*	*OD*	*OS*	*OD*	*OS*		*OD*	*OS*	
1, F, 32	8	OD	6/15−2	6/6	J5	J1†	–	–	–	–	2·3	0·7	ND	–	–	Idiopathic retrobulbar neuritis
2, F, 30	16	OD	3/60	6/6	<J14	J1	–	–	–	–	2·0	0·8	ND	–	–	Idiopathic retrobulbar neuritis
	54		6/6	6/6	J1	J1	–	–	–	–	1·3	0·7	ND	–	–	
	268		6/6−3	6/6	J1	J1	–	–	–	–	0·7	0·7	0·9	0·8	0·8	
3, M, 67	43	OU	6/60	6/60	<J14	<J14	–	–	–	–	1·75	3·13	1·7	1·1	1·8	Ethambutol/isoniazid retrobulbar neuritis
	200		6/18−2	6/18−2	J5−2	J5−3	Optic nerve pallor	Optic nerve pallor	–	–	1·5	2·2	2·8	0·5	0·8	
4, F, 39	14	OD	6/24+2	6/6	J10	J1†	Optic nerve pallor	–	–	–	1·8	1·1	1·1	1·6	1·0	Multiple sclerosis
5, F, 29	17	OS	6/6	6/120	J1	<J14	–	Optic nerve pallor	–	–	1·0	1·25	0·9	1·0	1·3	98 days between onset of attacks
	21§	OU	6/6	6/6−1	J1−1	J1−1	–	Optic nerve pallor	–	–	1·8	0·8	1·8	1·0	0·5	Idiopathic optic neuritis
6, F, 37	9	OS	6/6	6/30+2	J1	J3	Optic nerve pallor	–	–	–	0·8	1·0	ND	–	–	Idiopathic optic nerve pallor right eye; idopathic retrobulbar neuritis left eye
7, F, 19	6	OD	CF at 10 cm«	CF at 10 cm«	<J14	<J14	–	Optic nerve pallor	–	–	1·5	1·5	1·4	1·1	1·1	Systemic lupus erythematosus, right retrobulbar neuritis, left optic nerve pallor

* + Indicates present, – absent, ND not done.

† $\times 10^{-8}$ g/ml.

‡ Blood fluorescein concentration $\times 10^{-5}$ g/ml.

§ Second episode.

« CF=counting fingers.

Table 2 *Patients with evidence of disc oedema and/or hyperaemia clinically and/or by fluorescein angiography (cases 8-12) and control cases**

Case no. sex, age (yr)	*Days between visual loss and testing*	*Symptomatic eye*	*Best corrected visual acuity*				*Disc oedema and/or hyperaemia*		*Fluorescein angiography: late disc staining and/or leakage*		*Posterior vitreous fluorophotometry*					*Remarks*
			Distance		*Near*						*Uncorrected*†		*Bld*‡	*Corrected*†		
			OD	*OS*	*OD*	*OS*	*OD*	*OS*	*OD*	*OS*	*OD*	*OS*		*OD*	*OS*	
8, F, 26	5 16	OS OD	6/7·5−2	6/15+2	J1+	J1+	+	−	+	+	1·8	3·0	1·5	1·2	2·0	Idiopathic optic neuritis
9, F, 33	28	OD	6/30−2	6/7·5−2 +1	J5	J1	+	−	−	−	1·1	1·1	ND	−	−	Idiopathic optic neuritis
10, F, 41	12	OD	LP, no projection	6/7·5+3	<J14	J1	+	−	+	−	§	1·2	0·5	−	2·4	Idiopathic optic neuritis. Diagnosed as syphilis without central nervous system involvement
	51		CF at 70 cm	6/7·5−2	<J14	J1	Optic nerve pallor	−	−	−	1·5	2·0	1·5	1·0	1·3	
11, F, 58	30	OD	6/30−1	6/12+1	<J14	J1	+	−	+	−	1·9	1·4	ND	−	−	Presumed right sarcoid optic neuritis OD
	201		CF at 150 cm«	6/9+1	<J14	<J1+2	Optic nerve pallor	−	+	−	1·2	0·9	1·0	1·2	0·9	
12, M, 30	135	OU	CF at 5 cm«	CF at 5 cm«	<J14	J14	+	+	+	+	0·7	1·0	0·6	1·0	1·7	Grade III astrocytoma with obstructive hydrocephalus

* + Indicates present, − absent, ND not done.

† $\times 10^{-8}$ g/ml.

‡ Blood fluorescein concentration $\times 10^{-5}$ g/ml.

§ Patient unable to tolerate contact lens in this eye.

« CF=counting fingers.

more seriously affected eye if bilateral) immediately on injection, and photographs of both eyes were taken at 10 minutes. Anterior chamber fluorophotometry measurements were made on 8 patients (15 eyes) immediately after vitreous fluorophotometry at 1 hour (Table 2). Normal anterior chamber fluorophotometry in our laboratory gives $20{\cdot}9 \pm 12{\cdot}6 \times 10^{-8}$ g/ml.

Determination of the blood fluorescein concentration was performed in 9 of the 12 patients. Blood from a finger prick was aspirated into a 50 μl pipette and then diluted in 2 ml of saline. After centrifugation the fluorescein concentration was measured photometrically in the supernatant diluted plasma. From a study by one of the authors (J. G. C-V.), the posterior vitreous fluorophotometry readings taken 3·5 mm in front of the retina were corrected for a blood fluorescein concentration of 1×10^{-5} g/ml.[2] We used as a correction factor the ratio between the fluorescein concentration in the blood at 1 hour after injection and 1×10^{-5} g/ml.[2] In a recent series of 45 normal volunteers whose background vitreous fluorophotometry readings were corrected in accordance with fluorescein concentrations in the blood a value of $0{\cdot}49 \pm 0{\cdot}17 \times 10^{-8}$ g/ml (mean±SD) was obtained. In this article posterior vitreous fluorophotometry readings not normalised for blood fluorescein concentration are referred to as uncorrected posterior vitreous fluorophotometry values; normalised readings are referred to as corrected values. Corrected and uncorrected posterior vitreous fluorophotometry readings that were equal to or greater than 1×10^{-8} g/ml were considered abnormal.[3–5] (SI conversion: g/l=g/ml×10³.)

All patients had complete neurological and physical examinations (except case 1, which was lost to follow-up). Where indicated, diseases associated with optic neuritis and retrobulbar neuritis were excluded by appropriate investigation.

Results

RETROBULBAR NEUROPATHY

The symptoms and signs of retrobulbar neuritis were confirmed with increased posterior vitreous fluorophotometry readings. In cases 1, 2, and 6 these were uncorrected values; in cases 3 and 7 they were corrected readings. Cases 6 and 7 had evidence of optic nerve pallor in the contralateral eye. All cases had idiopathic retrobulbar neuritis except cases 3 and 7, which were, respectively, toxic retrobulbar neuropathy and systemic lupus erythematosus with right retrobulbar neuritis (Table 1).

OPTIC ATROPHY

Increased corrected posterior vitreous fluorophotometry readings confirmed the diagnosis of optic neuritis in 2 patients with optic atrophy in the symptomatic eye (cases 4 and 5) (Table 1).

DISC OEDEMA AND/OR HYPERAEMIA

As expected, clinical and/or angiographic evidence of disc oedema or hyperaemia was confirmed, with increased posterior vitreous fluorophotometry readings. In cases 9 and 11 this was demonstrated with increased uncorrected readings on posterior vitreous fluorophotometry. Bilateral confirmation was obtained with increased corrected posterior vitreous fluorophotometry values in cases 8 and 12.

Asymptomatic fellow eyes had increased uncorrected (cases 9 and 12) and corrected (cases 4, 5, 7, and 10) values on posterior vitreous fluorophotometry. The high incidence of bilaterally increased values on posterior vitreous fluorophotometry in patients with systemic or toxic causes is notable (case 3, toxic retrobulbar neuropathy; case 7, systemic lupus erythematosus optic neuritis; and case 11, presumed sarcoid optic neuritis). Case 10 had a diagnosis of syphilis with a positive serum fluorescent treponemal antibody test and positive serum Reiter protein reaction of 1:4 dilutions. The results from cerebrospinal cytology, protein estimations, and electrophoresis were normal, and the cerebrospinal fluid fluorescein treponemal antibody test was unreactive. Case 11, a 58-year-old black woman, was diagnosed as having presumed sarcoidosis with serum polyclonal gammopathy and serum angiotensin converting enzyme of 40 IU/l (normal: 10 to 30 IU/l),[6] cerebrospinal fluid pleocytosis, old right lower lobe granuloma on chest roentgenography, and optic nerve enlargement on computerised tomography (Fig. 1). The serum lysozyme level was 11·4 μg/ml (normal: 2·5 to 12·9 μg/ml). The results of a cervical lymph node biopsy were negative in this patient.

The anterior chamber fluorophotometry values at 1 hour after injection in 8 patients (15 eyes) were normal (Table 3). The mean anterior chamber fluorophotometry values for these patients were $19{\cdot}7 \times 10^{-8}$ g/ml (SD $6{\cdot}2 \times 10^{-8}$ g/ml). (SI conversion: g/l=g/ml×10³.)

Discussion

Vitreous fluorophotometry is a sensitive indicator of alteration of the blood-ocular barrier in diabetes and retinitis pigmentosa.[2 7] Isolated acute retrobulbar neuritis and acute retrobulbar neuritis associated with multiple sclerosis have been shown to alter the blood-ocular barrier reversibly.[1]

The present study was performed to investigate posterior vitreous fluorophotometry values in

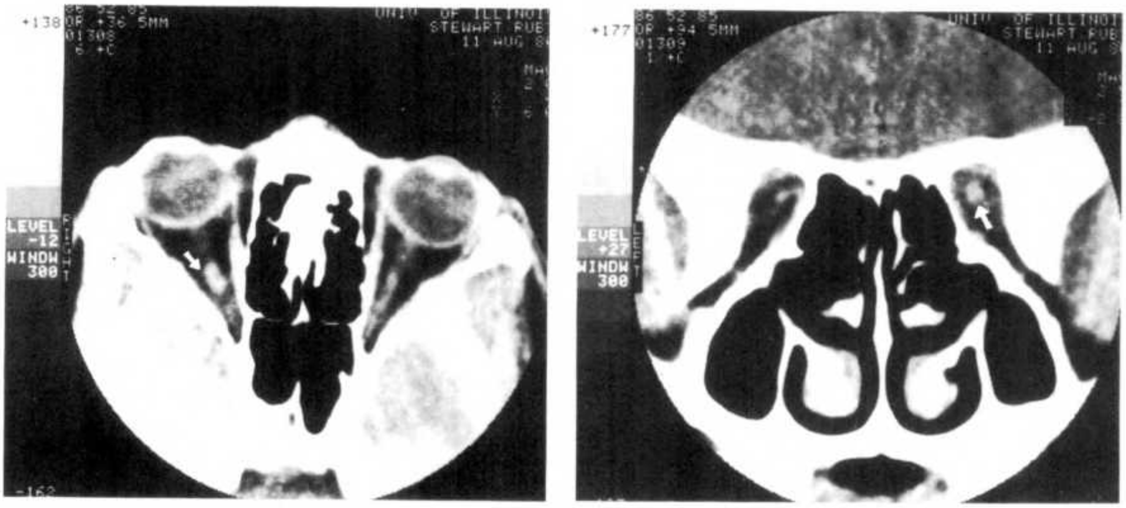

Fig. 1 *Case 11 has sarcoid optic neuritis. Note thickening of the posterior half of the right optic nerve (arrows) with apical soft tissue fullness around the optic nerve with contrast infusion on axial computed tomography (left) and on coronal computed tomography (right).*

patients with optic neuropathy with and without correction for variations in blood fluorescein concentration.[2] Although it is given in a weighted dose, fluorescein has been found to be present in lower levels in the blood of diabetic patients than in normal volunteers.[2] By normalising the posterior vitreous fluorophotometry value with the blood fluorescein concentration, the corrected posterior vitreous fluorophotometry reading is lowered if the fluorescein concentration in the blood is greater than 1×10^{-5} g/ml and increased if the concentration is lower than that level.[2]

RETROBULBAR NEURITIS

Increased corrected posterior vitreous fluorophotometry values in cases 3 and 7 confirm the previous findings of increased uncorrected posterior vitreous fluorophotometry readings in acute retrobulbar neuritis (cases 1, 2, and 6).[1]

Table 3 *Anterior chamber fluorophotometry readings at 1 hour*

Case	*Days between visual loss and testing*	*Anterior chamber fluorophotometry**	
		Right eye	*Left eye*
2	268	11·0	9·0
4	14	29·0	22·0
5	17	14·5	17·0
	21†	30·0	28·0
7	6	14·0	14·0
9	28	20·0	19·0
10	12	‡	25·0
11	201	23·0	22·0
12	135	19·0	19·0

* $\times10^{-5}$ g/ml.
† Second episode.
‡ Patient unable to tolerate contact lens in this eye.

Case 3 demonstrates retrobulbar neuropathy due to ethambutol/isoniazid toxicity without vitamin B_6 supplementation. The patient was aphakic 8½ years before the onset of visual impairment. Three months before referral the distance visual acuity had been 6/6-1 on the right and 6/7·5-2 on the left. The dosages were 300 mg/day of isoniazid and 1200 mg/day of ethambutol for 13 months until 17 days after the bilaterally decreased visual acuity had been appreciated subjectively. He was referred to us 43 days after subjective visual loss, when distance vision was 6/60 bilaterally. The diagnosis of retrobulbar neuropathy secondary to drug toxicity was confirmed by the bilaterally increased corrected posterior vitreous fluorophotometry values. The patient was started on a regimen of multivitamins and pyridoxine from the day of referral. After 6 months the distance visual acuity had improved to 6/18-2 bilaterally. The corrected posterior vitreous fluorophotometry values at this time had returned to normal.

OPTIC ATROPHY

Optic nerve pallor indicates previous optic nerve disease and may be associated with little or no disc oedema, depending on the degree of axonal degeneration. Persistent visual evoked response abnormalities may also preclude a diagnosis of acute retrobulbar neuritis in a patient with previous optic neuritis, as abnormalities of the visual evoked response can persist for at least 5 years.[8] Prolongation of latency of a previously increased visual evoked response or decreased amplitude may provide helpful evidence in these cases. Cases 4 and 5 had increased corrected posterior vitreous fluorophotometry values in the symptomatic eyes, which indicated altered permeability of the blood-ocular barrier together with optic atrophy.

DISC OEDEMA AND/OR HYPERAEMIA

Evidence of disc oedema from ophthalmoscopy or fluorescein angiography or both was confirmed with corrected posterior vitreous fluorophotometry values in cases 8 and 12. In addition to providing objective confirmation of disc oedema and/or hyperaemia, posterior vitreous fluorophotometry measures leakage and can be helpful in (1) evaluating the progression of disease and response to treatment; (2) differentiating cases that are difficult to differentiate from normal papillary and peripapillary fluorescence on fluorescein angiography; (3) assessing asymptomatic fellow eyes (cases 4, 5, 9, 10, and 11); and (4) assessing asymptomatic fellow eyes in patients with retrobulbar neuritis.[1]

Vitreous fluorophotometry values tend to become normal in approximately 7 weeks in patients with acute retrobulbar neuritis with or without multiple sclerosis.[1] Case 2 showed a persistently increased uncorrected value on posterior vitreous fluorophotometry at 54 days. The increased value in this case may relate to persistent symptoms, persistent central Amsler grid distortion, and colour desaturation of the right eye despite 6/6 distance visual acuity. Presumed sarcoid optic neuritis (case 11) is an additional factor that may prolong permeability of the blood-ocular barrier at 6 months and longer following the onset of symptoms. Anterior chamber fluorophotometry, if increased, could be valuable to reinforce the possibility of a systemic cause altering both the blood-aqueous and the blood-retinal barriers. However, no increased anterior chamber fluorophotometry was noted in the 8 patients studied (Table 3).

Sarcoidosis was the presumptive diagnosis in one case. In a recent review 5% of patients with sarcoidosis were found to have neurological manifestations, and the optic nerve has been shown to be the second most frequently involved cranial nerve.[9] Computerised tomography has been valuable in detecting optic neuritis and retrobulbar neuritis.[10–12] One recently reported case of sarcoid retrobulbar optic neuropathy[13] failed to show any computerised tomographic abnormality. The optic neuritis of case 11 showed thickening of the posterior half of the right optic nerve and inflammatory reaction replacing fatty tissue at the orbital apex on computerised tomography (Fig. 1). Thus the infiltrative ophthalmopathy of a granulomatous disease noted clinically, angiographically, and on computerised tomography (case 11, right eye) was confirmed by vitreous fluorophotometry. The increased vitreous fluorophotometry value in the asymptomatic eye was shown objectively only by a distance visual acuity of 6/12+1. The distance vision subsequently improved one line (Snellen chart) in this asymptomatic eye, with a return to normal of the vitreous fluorophotometry value.

We believe that vitreous fluorophotometry measurements are valuable in diagnosing inflammatory, obstructive, and infiltrative optic neuropathies when conventional fluorescein angiography is normal. Concurrent anterior chamber fluorophotometry readings were not increased in the cases studied, but it seems possible for anterior chamber fluorophotometry readings to be raised without any biomicroscopic disease in the anterior segment when there is a systemic cause of the optic neuropathy, thus indicating a generalised rather than localised aetiology. Another clue to systemic pathology is persistently increased values on vitreous fluorophotometry but persistent symptoms—for example, central scotoma—which may blur the distinction between residual optic nerve damage, recurrence, and continuing systemic disease.

This study was supported by a grant from the Kroc Foundation, Santa Ynez, California, and Core Grant EY01792 from the National Institutes of Health, Bethesda, Maryland.

We thank Ms J. Halik for typing the manuscript.

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British Journal of Ophthalmology, 1982, **66**, 567–568

Report on the presence of a toxic substance, dimethyl formamide, in sodium fluorescein used for fluorescein angiography

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SUMMARY The revelation that intravenous sodium fluorescein is not all that it might seem to be may be a significant finding in the light of the adverse reactions to fluorescein that have been previously reported. Analysis of commercially prepared intravenous sodium fluorescein by mass spectroscopy and nuclear magnetic resonance has indicated that an industrial solvent used in the manufacturing process has not been eliminated. Dimethyl formamide is an industrial solvent with a maximum acceptable exposure level of 10 parts per million for dermal contact. It has been found in quantities of 5000 parts per million in the fluorescein for intravenous use. This investigation was prompted by a significant increase in the adverse reactions in patients receiving intravenous fluorescein in the retinal photographic unit at the Manchester Royal Eye Hospital.

Fluorescein, [spiro (isobenzofuran—1 (3H), 9′—(9H)=xanthem]—3—one—3′6′ dihydroxy, is made by heating phthaleic anhydride with resorcinol. It is a yellowish red powder which is soluble in water, alcohol, glycerol, dimethyl formamide, and 85% formic acid, but is insoluble or very sparingly soluble in chloroform, ethyl ether, benzene, and xylene. The sodium salt, molecular weight 376.27, is freely soluble in water and gives an intense yellowish green fluorescence in blue or ultraviolet light down to a concentration of 0·02 ppm.[1]

An aqueous solution of sodium fluorescein given intravenously now forms a major part of the assessment of many retinal disorders. 5 ml of 10% or 3 ml of 20% or 25% solution is injected rapidly intravenously. It is adsorbed on to albumin and other plasma proteins in the blood stream and thus circulates to the eye. The fluorescein is excited within the eye by means of a blue illuminating light, and a photographic record of its passage through the eye is obtained through a yellow-green barrier filter.

Excretion of fluorescein from the body is in urine in a mainly unchanged form, but in part it is conjugated and eliminated by the liver.

Adverse side effects of intravenous fluorescein injection are well documented and include nausea, vomiting, and urticaria as well as some more severe 'anaphylactoid' reactions of laryngeal oedema or even shock and cardiac arrest. The overall incidence of side effects is 10 to 20% for nausea, 0·1 to 1·4% for urticaria and vomiting, and 0·6 to 1% for severe reactions.[2]

Materials and methods

At the Manchester Royal Eye Hospital a record of adverse reactions to intravenous fluorescein administered in retinal photographic investigations has been routine. Concern was raised recently when an increase from 6·8% for January to July 1980 to 12·7% for January to July 1981 was noted in the *total number* of adverse reactions (Table 1). At the same time the severity of the reactions had increased. These have in order of severity consisted of one case of acute 'anaphylactoid' shock, effects on the central nervous system resulting in one case of temporary deafness, complaints of back pains, and several cases of nerve pains in the arms. In addition there was a marked increase in the frequency of nausea and the severity of the vomiting.

The technique of performing fluorescein angiography had not changed; however, a different batch of fluorescein was being used. Consequently a chemical analysis of the fluorescein was performed to see if an explanation could be found for the increase in the adverse reactions.

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Table 1 *Adverse reactions to 3 ml of 25% fluorescein intravenously*

	1980			*1981*		
	Total no. of fluorescein angiograms	*No. of reactions*	*% Reactions*	*Total no. of fluorescein angiograms*	*No. of reactions*	*% Reactions*
January	118	7	5·9	154	23	14·9
February	127	10	7·8	150	17	11·3
March	130	3	2·3	149	17	11·4
April	102	14	13·7	134	17	12·7
May	62	5	8·1	91	16	17·6
June	145	9	6·2	68	13	19·1
July	163	10	6·1	109	10	9·2

This analysis revealed the presence of a significant amount of an industrial solvent, dimethyl formamide (DMF), in the fluorescein. The DMF was detected by mass spectrometry and measured by nuclear magnetic resonance spectroscopy. Two samples of 25% sodium fluorescein showed 11% and 8·5% molar DMF with respect to fluorescein. A sample of 20% sodium fluorescein from the same manufacturing source showed a similar percentage of DMF. Two samples of 25% sodium fluorescein from a different source made up in our own hospital pharmacy showed no evidence of DMF.

Discussion

DMF is used in the purification to pharmaceutical standards of crude sodium fluorescein, and it would appear that the incomplete removal of the solvent from the finished powder was responsible for the adverse reactions. DMF is a substance readily absorbed following inhalation or skin contact, and is *not* intended for intravenous infusion. At lower levels of exposure to DMF by inhalation, direct contact or ingestion, nausea, and vomiting may result. Neurotoxicity, abdominal pain, hepatomegaly, hepatic necrosis, and kidney damage are seen in higher levels of exposure.[3]

Attempts to find a cause for the adverse reactions to fluorescein in the past have also pointed to impurities in the sodium fluorescein. Yannuzzi *et al.*[4] found following chromatographic analysis that the presence of impurities increased the incidence of commonly reported side effects of fluorescein. The presence of small amounts of DMF, however, is not readily detected by chromatographic analysis, the use of sophisticated columns being required. Nor is DMF identifiable by fluorescent analytical techniques. Other workers[2] attempted to find an allergic cause for the reactions but with limited success.

Further work would have to be done to link DMF directly with the increased number of adverse reactions to fluorescein. However, the presence of DMF, a toxic contaminant in the fluorescein used in the January to July 1981 batches cannot be disputed. Since reverting to the use of purified 25% sodium fluorescein with confirmed absence of DMF, a sequence of 256 cases has shown none of the violent adverse reactions previously experienced with the contaminated batch. The incidence of nausea and vomiting reactions reverting to around 5%.

Following notification of the DHSS, users of fluorescein have been circularised warning of the content of DMF in certain batches of the dye. Regulations controlling the permissible exposure to DMF are at present under review. Subsequent to our discovery DMF in fluorescein for intravenous use has been eliminated by obtaining correctly purified sodium fluorescein.

The authors express their sincere thanks to Messrs ICI (Organics) for their invaluable assistance in the analysis of the various samples of sodium fluorescein and to Sister A. Goodfellow and Mrs G. Shawcross of the Retinal Medical Service at the Manchester Royal Eye Hospital for providing statistics and samples from which the authors were able to carry out their investigation.

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British Journal of Ophthalmology, 1982, **66**, 569–572

Use of portable vitrectomy instrumentation (VISC X) in the rural Guatemalan highlands

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SUMMARY In a rural mountain setting 20 patients with blinding ocular opacities were treated surgically with modern vitrectomy techniques. There were no intraoperative or postoperative complications unique to the isolated environment. Because of its compact portability, the VISC X proved to be an ideal vitrectomy instrument. In addition to plastic lid procedures, cataract extraction, and strabismus surgery, repair of retinal detachment and vitrectomy in selected cases has been added to the armamentarium of surgeons who are seriously involved in exporting ophthalmology to remote places.

In 1978 we reported an improvised technique using liquid nitrogen for the treatment of retinal detachment in the rural Guatemalan Highlands.[1] In 1979 we returned to the Hospital Jacaltenango in Guatemala on a repeat medical and surgical expedition. This time we took a light-weight, portable, battery operated vitrectomy instrument (VISC X)[2] in anticipation of selected cases in which it might be useful. In a period of 9 days we used the VISC X in the management of 20 cases which otherwise would have been inoperable or more difficult to manage (Table 1). We present here the indications and methods of vitrectomy instrument surgery which we found useful in the rural setting of ophthalmic care.

Table 1 *Indications for vitrectomy instrument surgery in Guatemala, 1979*

Indication	*Number of cases*
1. Congenital cataract	7
2. Traumatic cataract	3
3. Secondary cataract	5
4. Vitreous haemorrhage and debris	2
5. Removal of extracapsular cataract remnants	2
6. Pupillary membrane	1
7. Management of vitreous loss in cataract surgery	0
8. Augmentation to retinal detachment surgery	0

Patients and methods

The 20 patients were selected for surgery from approximately 600 outpatients seen during our 9 days in Jacaltenango. Patients arrived on foot, horseback, or were carried from as far as 100 kilometres for eye examination and treatment. All patients were, for the most part, Mayan Indians. The area from which they came is north-western Guatemala, and the primary geographic feature is steep volcanic mountains and sequestered valleys (Figs. 1, 2). In some areas trachoma and tuberculosis are endemic. Malnutrition is ubiquitous.

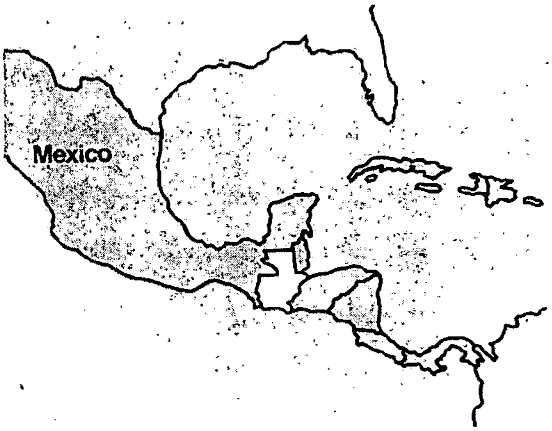

Fig. 1 *Guatemala is the first country in Central America south of Mexico.*

Correspondence to James D. Kingham, MD, 1830 S. Osprey Avenue, Sarasota, Florida 33579, USA.

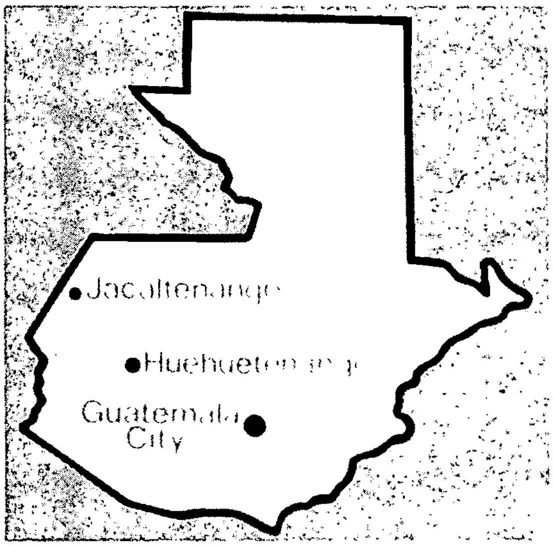

Fig. 2 *Jacaltenango in north-western Guatemala is 346 km up the Pan American Highway from Guatemala City and across 2 mountain ranges.*

All operations were done in a small hospital operating room under aseptic and sterile conditions. Local anaesthesia was used in all cases. Most cases were done under observation with the Codman portable operating microscope, but one pars plana vitrectomy was done under visualisation with the indirect ophthalmoscope. Balanced salt solution or Ringer's lactate solution was used as infusion.

All operations were performed by a surgeon experienced in retinal and vitreous surgery (J.D.K.) or corneal and external surgery (R.H.P.). All operations were done through a small incision at the corneoscleral limbus with the exception of 2 cases done through the pars plana. The surgical technique was straightforward and standardised and has been previously described using such various vitrectomy instrumentation as the Machemer-Parel VISC,[3] Douvas Rotoextractor,[4] and Peyman vitrophage.[5 6]

The following case reports are representative of the types of surgery which were performed.

Case reports

Cases 1 and 2. Congenital cataract and removal of extracapsular cataract extraction remnants. A 23-year-old man had bilateral congenital cataracts which had become progressively worse since early childhood. He had no nystagmus. Vision was light perception in both eyes. He had a planned extra-capsular cataract extraction in his right eye which resulted in excessive residual cortical material in the anterior chamber. On the second postoperative day the cortical material was removed with the VISC. One day later the dense cataract was removed from his left eye with the VISC. The next day the media were clear in both eyes, with a good red reflex. With aphakic correction subjective vision had improved dramatically in both eyes.

Case 3. Traumatic cataract. A 27-year-old man had been kicked in the face by an ox 4 years previously, with a resultant dense traumatic cataract in his left eye. An agricultural worker, he was considered an excellent candidate for a planned extracapsular cataract extraction by VISC technique, primarily for return of full visual field. The lens was removed with the VISC leaving an intact posterior capsule. Postoperatively, without aphakic correction, subjective vision and visual field were improved.

Case 4. Secondary cataract. A 43-year-old widow, long afflicted with tuberculosis, lived an isolated life in a small hut with 2 children. She had a blind phthisical right eye and only light perception in her left eye. The left pupil was miotic and secluded and there was a dense cataract. Corneal keratic precipitates and hypotony suggested an inflammatory aetiology for the secondary cataract. A tuberculous aetiology was postulated for the uveitis. The lens was removed with the VISC through a limbal incision after synechiolysis. The posterior capsule was left intact. Five days postoperatively vision had improved to hand movements.

Case 5. Pupillary membrane. A 62-year-old man had unplanned extracapsular cataract surgery 12 years previously with subsequent dense pupillary membrane and updrawn pupil in his right eye. Vision was light perception. A mature cataract was present in his left eye. Two days after uneventful and successful intracapsular cataract extraction in his left eye the pupillary membrane in the right eye was excised with the VISC. With aphakic correction subjective vision was improved dramatically in both eyes on the second postoperative day.

Case 6. Vitreous haemorrhage. A 26-year-old man had dense vitreous haemorrhage in his right eye. The left eye showed perivascular sheathing and intraretinal haemorrhages. Vision was hand movements in the right eye and 20/25 in the left eye. The diagnosis was periphlebitis retinae (Eales's disease). A pars plana vitrectomy was done with the VISC under observation with the indirect ophthalmoscope, with adequate clearing of a central core of blood. Postoperatively he had diffuse blood in the vitreous cavity, which was expected to clear. Subjective vision was slightly better than before operation.

Case 7. Vitreous debris and cyst from uveitis. A 33-year-old man had vision of 20/40 in his right eye and counting fingers at 6 feet (1·8 m) in his left eye. The left eye had diffuse vitreous debris with a large mobile spherical lesion about 6 disc diameters in size. A pars plana vitrectomy was done under observation with the operating microscope. The spherical lesion similar to the intra-vitreous cysticercus described by Hutton *et al.*[7] was removed with ease along with the cloudy vitreous. An iatrogenic posterior retinal tear was treated with injection of air and drainage of subretinal fluid. Postoperatively we could not determine the status of the retina at the time we left.

Results

All patients who underwent surgery with the VISC X experienced subjective visual improvement except an 11-year-old boy with secondary cataract who postoperatively was found to have a retinal detachment (an attempt was made to repair the retinal detachment) and the above mentioned patient (case 7) who developed an iatrogenic retinal detachment. One additional patient was found after lensectomy to have a retinal detachment, which was successfully repaired. In most patients subjective vision was expected to continue to improve.

Quantitative postoperative visual acuity was difficult to assess, as the duration of field activity was limited to 2 weeks. However, follow-up care was continued through paramedical personnel and by the mission medical doctors (M.A. and D.E.). The use of graphic quiz games has proved mostly unsuccessful for us in assessing either preoperative or postoperative vision in the illiterate Guatemalan Indians, prompting us to evaluate the Arden grating test in future field work.

Discussion

Cataract surgery, enucleation, and lid surgery are commonly performed in remote rural areas.[8 9] Recognising retinal detachment as a complication of cataract surgery in 2–3% of cases,[10] we improvised a method while in Guatemala of treating retinal detachments with cotton tip sponges dipped in liquid nitrogen for cryosurgical adhesion.[1] Encouraged by our initial success we decided to increase our surgical capabilities by taking a portable vitrectomy instrument. To our surprise we found more patients than we had expected in whom surgery with the VISC would be beneficial, or in some cases absolutely necessary.

We believe cataract removal with the VISC produced superior results than had we done standard extracapsular cataract extractions in traumatic or secondary cataracts, especially in young patients. The extracapsular removal of congenital cataracts was facilitated by the VISC, and in no case did we encounter vitreous loss or difficulty removing residual cortex, as had been our experience previously. Clearly, vitreous haemorrhage cannot be cleared by any other surgical treatment. Removal of pupillary membranes by the VISC is a well documented procedure,[11] and indeed in our hands is the method of choice. Furthermore the 2 patients who were found to have previously undiagnosed retinal detachments were benefited, after lensectomy, by having subsequent retinal reattachment surgery. In these cases the operative site was secure and there was little concern over wound dehiscence as would have been the case in standard large-wound extracapsular techniques.

Although we did not use the VISC to remove anterior vitreous associated with vitreous loss at cataract extraction, this certainly would be an added indication, as well as the use of pars plana vitrectomy to augment the management of vitreous traction in difficult cases of retinal detachment.[12]

The vitrectomy instrument chosen for this expedition, the VISC X, suited our purposes admirably. It is compact and battery operated, can be autoclaved, is easily portable in its packing box with dimensions of 38×63×71 cm (15×25×38 inches), and light weight, with a total packed weight of 15 kg (33 pounds).

We believe that our experience with the VISC X in a remote rural setting adds another dimension to the overall clinical capabilities of visiting ophthalmic field teams and underscores the practicality of the concept of 'exporting ophthalmology'.[13] It is now possible to transport light weight microscopes and vitrectomy instrumentation to remote areas that have no access to ophthalmic surgery. We would like to emphasise that this is difficult and exacting microsurgery under the best of conditions. Needless to say, conditions in remote rural areas are much less than ideal, and surgery such as this should be undertaken only by those surgeons who are experienced in the technique of retinal and vitreous surgery and who are prepared and qualified to deal with real and potential complications.

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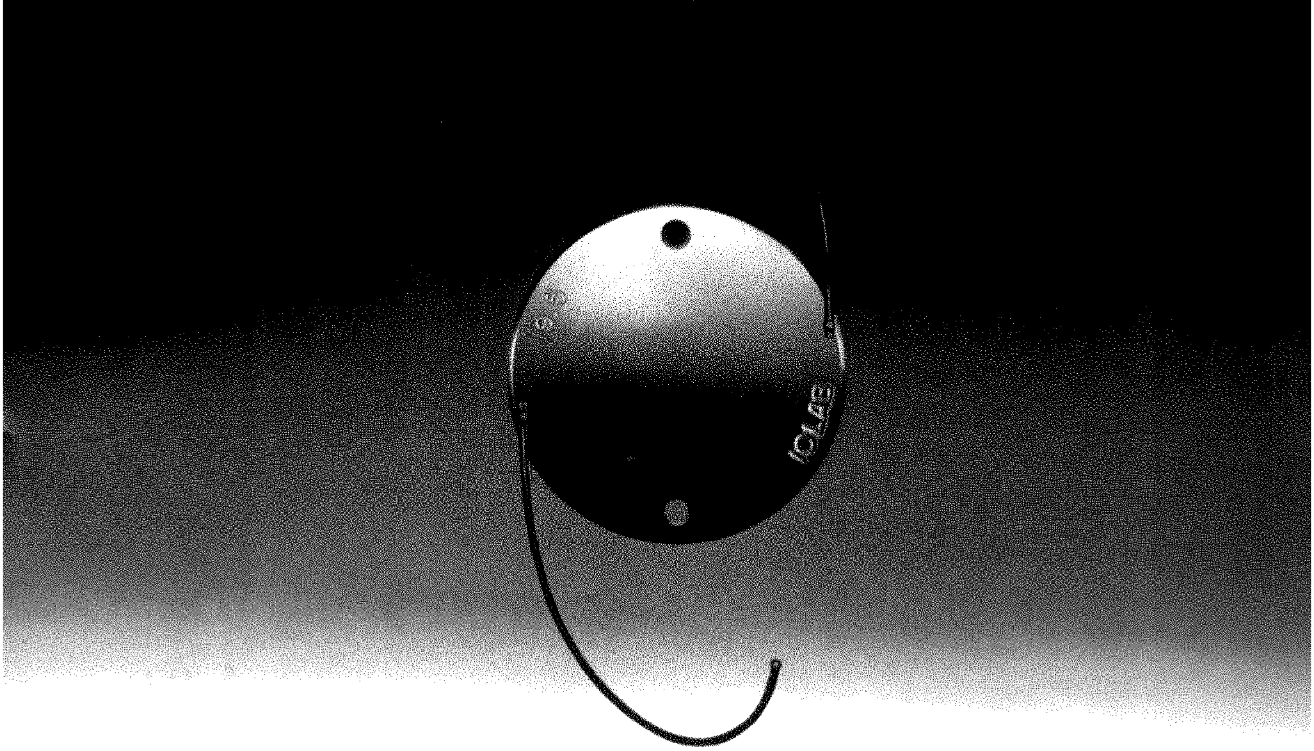

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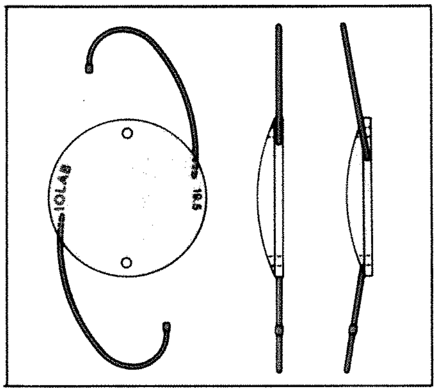

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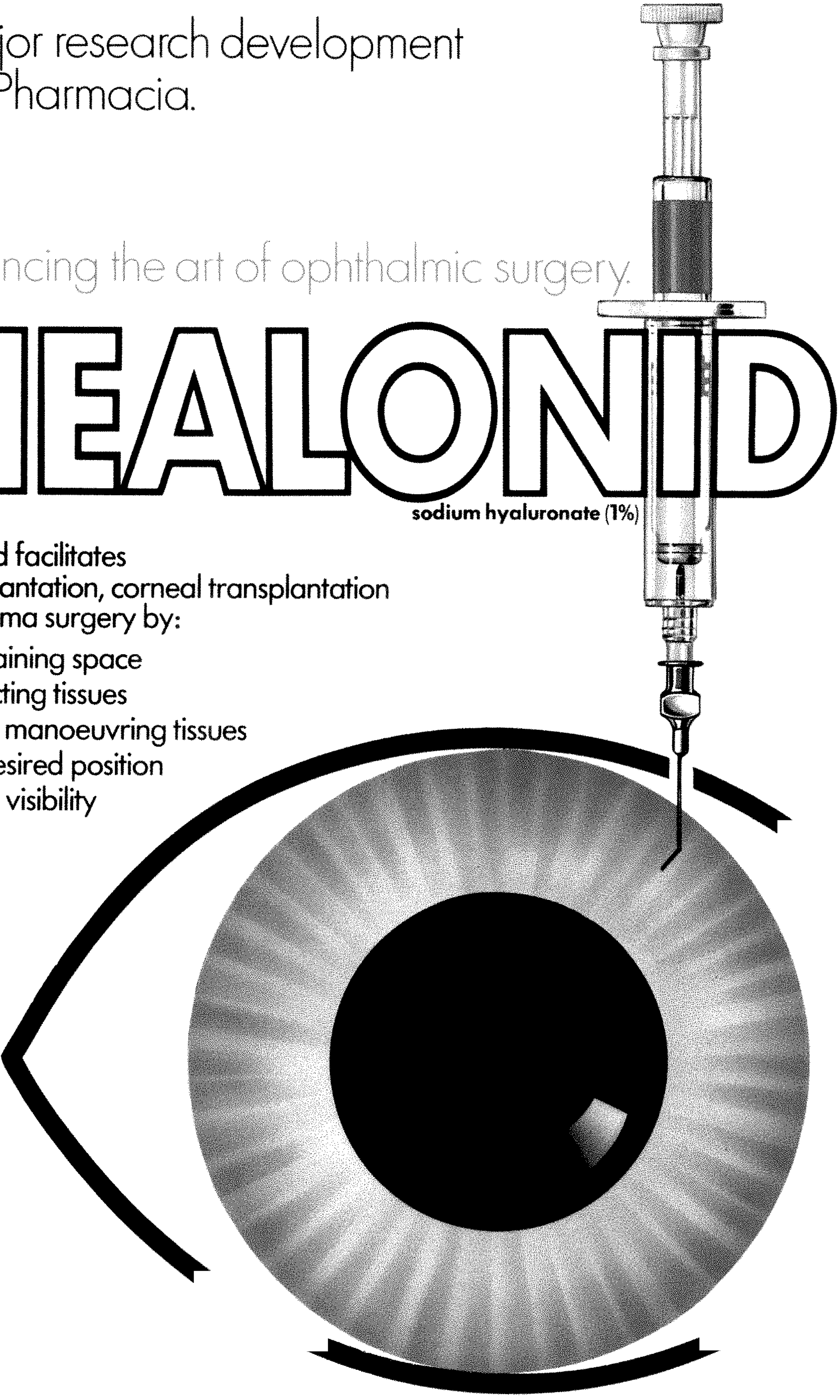

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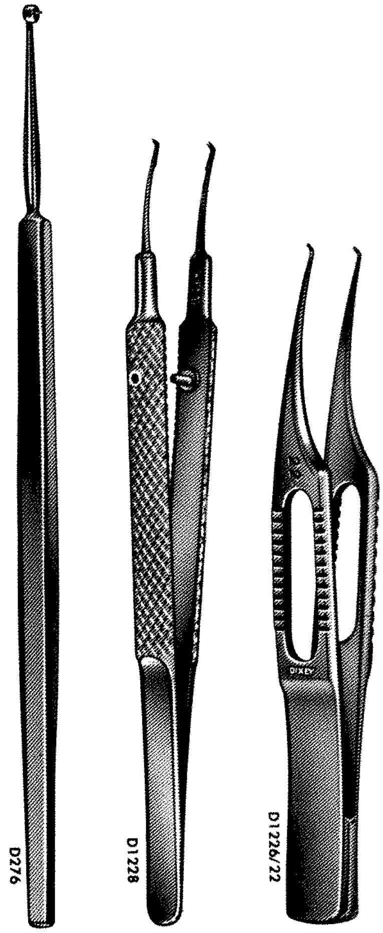

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British Journal of Ophthalmology, 1982, **66**, 573–575

Ophthalmological study of epidemic dropsy

M. K. RATHORE

From the Gandhi Medical College and Hamidia Hospital, Bhopal (MP), India

SUMMARY An ophthalmological study of a series of cases of epidemic dropsy in a recent outbreak in Madhya Pradesh was carried out. The present communication reports superficial retinal haemorrhages in epidemic dropsy, an observation believed not to have been previously reported.

Although epidemic dropsy was recognised in 1877 when it appeared as an epidemic outbreak in Calcutta, it came to the attention of ophthalmologists only in 1909, when Maynard[1] reported the occurrence of glaucoma in cases of the disease.

Epidemic dropsy is an acute toxic disease characterised initially by gastrointestinal disturbances, low-grade fever followed by oedema of the extremities, especially of the lower limbs (Fig. 1), with redness of skin, pain, and burning sensation over the oedematous part, symptoms of cardiac decompensation and breathlessness, and glaucomatous changes in the eyes. In some cases renal failure and cardiac failure may lead to death.

It is well established that contamination of cooking oil with seeds of *Argemone mexicana* is the cause of this toxic state. The seeds contain sanguinarine hydrochloride, an alkaloid of the benzphenathrine subgroup of the isoquinoline group.[2]

The mode of action of sanguinarine is not clearly understood. It appears to depress the action of sympathetic stimulation and of adrenaline. It also decreases to some extent the action of acetylcholine. In epidemic dropsy it is thought to block the sulphydryl radical of the main enzyme (co-ASH) responsible for pyruvate oxidation, thereby increasing the amount of pyruvate in blood.

Pathologically sanguinarine hydrochloride gives rise to dilatation and engorgement of capillaries in various tissues of the body. Gross capillary dilatation is seen in the uveal tract, particularly in the ciliary body.

Patients and methods

Fifty eyes of 25 clinically proved cases of epidemic dropsy were studied in an outbreak in June-July 1980. All of them belonged to the Bengali colony of Itarsi, a city in Madhya Pradesh, which was the only affected area. Bengalis who mainly consume mustard oil (which is readily contaminated with the seeds of *Argemone mexicana*) suffered from the disease, while the rest of the city's population remained unaffected. Oil samples taken from some of the affected families were positive for the presence of sanguinarine.

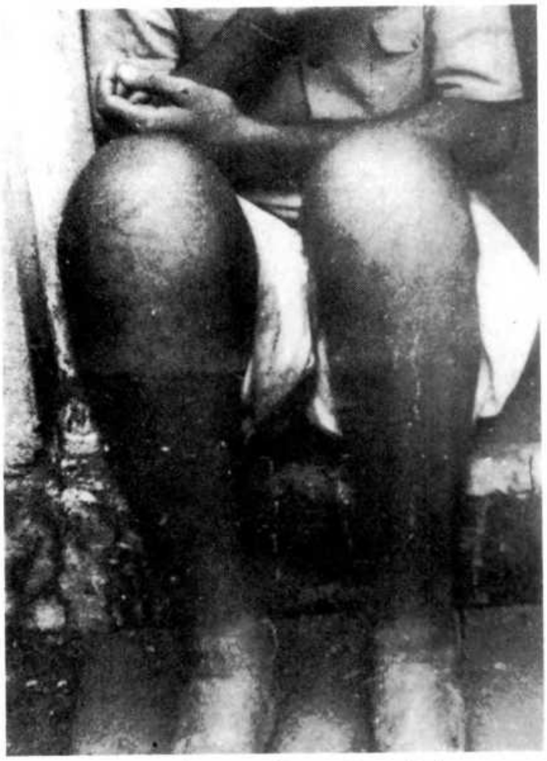

Fig. 1 *Epidemic dropsy: oedema of lower limbs.*

Ophthalmic examination carried out in the affected colony included recording of visual acuity, external ocular examination, measurement of intraocular

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tension with Schiøtz tonometer, and fundus examination.

Results

Sex distribution. A nearly equal incidence of the disease was observed in each sex (Table 1).

Table 1 *Sex distribution of cases*

	No.	*%*
Male:	13	52
Female:	12	48
Total:	25	

Table 2 *Age distribution of cases*

Age (years)	*No.*	*%*
Up to 10	1	4
11 to 20	8	32
21 to 40	10	40
41 to 60	5	20
Above 60	1	4

Table 3 *Visual acuity in 50 eyes*

VA	*No. of eyes*	*%*
6/6–6/12	47	94
6/18–6/36	0	0
6/60 or less	3	6

Table 4 *Intraocular pressure in 50 eyes*

Pressure (mmHg)	*No. of eyes*	*%*
Below 22	48	96
23 to 50	0	0
Above 50	2	4

Table 5 *Fundus findings in 50 eyes*

Fundus findings	*No. of eyes*	*%*
Normal	8	16
Retinal venous engorgement without any haemorrhage	32	64
Retinal venous engorgement with haemorrhage	10	20
Disc changes	0	0

Age distribution. Adolescents and young adults were relatively more affected. No case was seen below the age of 4 years, and the incidence was again less above the age of 60 years (Table 2). Similar observations were made by Sainani.[3]

Visual acuity. Most of the cases had normal visual acuity without glasses or with pin hole. Three eyes had visual acuity of less than 6/60. The cause of defective vision in 2 of them was lenticular opacities. In one patient who had macular haemorrhage the visual acuity was reduced to finger counting at 1 foot (30 cm) (Table 3).

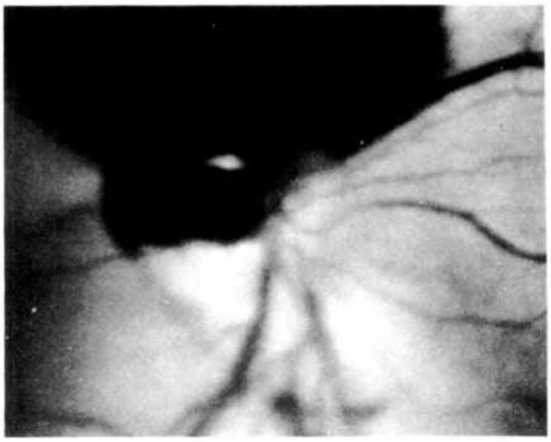

Fig. 2 *Right eye: superficial blot haemorrhage over the disc in case of epidemic dropsy.*

Intraocular pressure. In most of the eyes (96%) this was within normal limits (Table 4). Only one case had an intraocular pressure of 64 mmHg, but even with this pressure there were no congestive features.

Fundus findings. Fundus examination showed features of toxic vasculitis and venous engorgement in 84% of the eyes. 20% of them had superficial retinal haemorrhages of variable size scattered over the fundus (Table 5) (Figs. 2, 3). It was also observed that the severity of the epidemic dropsy (generalised symptoms and signs) was fairly closely related to retinal venous engorgement. Cases with mild or low-grade symptoms had no venous engorgement, while

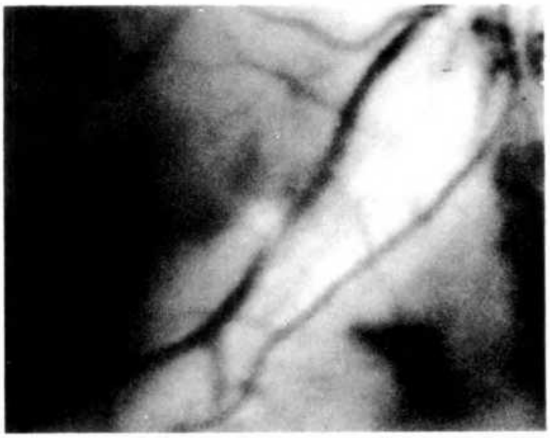

Fig. 3 *Inferotemporal area of same eye as in Fig. 2: congested retinal veins and superficial haemorrhages.*

subacute type of cases showed engorgement of the retinal veins. Acute fulminating cases had venous engorgement together with haemorrhages.

In 2 eyes initially there was only venous engorgement, but after 2 weeks, when they were admitted in the Medical College Hospital for symptoms of toxic myocarditis, they further showed retinal haemorrhages.

Discussion

The incidence of glaucoma in cases of epidemic dropsy is variable. In some epidemics it has been the dominating feature—10 to 12%[4 5]—while in other epidemics clinical findings other than glaucoma were noted.[3 6 7] In our series the incidence of glaucoma was relatively low, namely 4%. The mechanism of its production is not clearly understood. Hakim[8] in his experimental studies found ocular changes similar to those in chronic simple glaucoma. Leach[9] found proliferation of the endothelial lining of trabeculae in monkeys. Some other workers consider that the rise in ocular tension is due to the action of sanguinarine on the central nervous system.[10]

Shah[7] observed early venous congestion in 10 cases out of 67 (15%). A very high incidence of venous congestion was seen in our series (84%), probably as a part of generalised telangiectatic dilatation of capillaries which may be due to a histamine-like action of sanguinarine hydrochloride.

Superficial retinal haemorrhages occurred as a result of toxic vasculitis in 20% of cases. They appear to be due to toxic action of sanguinarine on blood vessels, particularly on veins. A similar type of haemorrhages was seen in liver, kidney, and other organs of the body on necropsy in some cases and experimentally in monkeys (Mishra N.P., personal communication). Papilloedema has been reported in 2 out of 119 (1·7%) cases[3]; it was not seen in any of our cases.

I am grateful to Dr Santokh Singh, Dean and Head of the Department of Ophthalmology, Gandhi Medical College, Bhopal, for his valuable guidance. I am also thankful to my colleague Dr S. C. Tiwari for his help.

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British Journal of Ophthalmology, 1982, **66**, 576–579

Behaviour of the fellow eye in acute angle-closure glaucoma

R. S. EDWARDS

From the Birmingham and Midland Eye Hospital, Church Street, Birmingham B3 2NS

SUMMARY A retrospective study of 245 fellow eyes of patients admitted in primary acute angle-closure glaucoma (ACG) is presented. Twenty-five (10·2%) had acute ACG in the fellow eye on presentation. Of the remaining 220, 33 (15%) subsequently developed acute ACG before prophylactic surgery was performed. Possible predisposing factors were analysed. The main findings were that acute ACG in the fellow eye occurred most frequently in hospital, or during the first month after discharge if prophylactic surgery was not performed. The instillation of mydriatics in the operated eye increased the risk to the fellow eye. Pilocarpine and carbonic anhydrase inhibitors confer the best protection on the fellow eye, but no medical regimen entirely prevented an attack of acute ACG in the fellow eye.

The aim of this retrospective study was to determine the behaviour of the fellow eye in patients admitted with primary acute angle-closure glaucoma (ACG). The possible factors which might precipitate acute ACG in this eye have been studied.

The consequences of an attack of acute ACG are well documented. They include peripheral field loss from ischaemic damage to the optic nerve head,[1] some loss of visual acuity[2] even if the attack is treated at its inception,[3] and a lowering of endothelial cell density in attacks which last 3 days or more.[4] It is therefore advisable to prevent an attack of acute ACG in the fellow eye whenever possible.

Patients and methods

Two hundred and forty-five patients admitted as emergencies to the Birmingham and Midland Eye Hospital in primary acute ACG during the period of January 1972 to December 1978 were studied. Patients with chronic angle closure were excluded, and all the fellow eyes had narrow angles. One hundred and seventy (69%) were female and 75 (31%) male, their mean age being 66·8 years.

The incidence and timing of acute ACG attacks in the fellow eye were studied and the risk to the fellow eye during the periods outlined in Table 1 has been expressed in terms of attack rate, or the number of attacks of acute ACG per 100 fellow eyes per day.

$$\text{Attack rate} = \frac{\text{percentage of fellow eyes developing acute ACG}}{\text{number of days in period studied}}$$

The following factors were investigated: the general health and systemic medication of all patients at presentation; the topical and systemic medication prescribed pre- and postoperatively, on discharge, and during the follow-up period.

Although individual treatment regimens varied greatly, it was possible to group them according to the strength and frequency of pilocarpine instillation in the fellow eye and according to whether or not a mydriatic was instilled in the operated eye. Mydriatics to the operated eye included atropine 1%, Mydrilate (cyclopentolate HCl) 1%, phenylephrine 10%, and homatropine 2% instilled one to 3 times a day. Comparisons were made in each case between patients whose fellow eye developed acute ACG and patients whose fellow eye escaped acute ACG.

Results

Incidence of attacks. Fifty-eight patients (23·6%) developed an attack of acute ACG in the fellow eye

Table 1 *Surgical management of the fellow eye*

Management	*No. of patients*
Surgery simultaneously with acute eye	51
Separate operation while still in hospital	142
Discharged from hospital without surgery	52
Total	245

Correspondence to Mr R. S. Edwards

Table 2 *Details of fellow eyes developing acute attacks*

Timing	*Number prior to surgery*	*Number developing acute ACG*	*Percent*	*Attack rate (no. of attacks per 100 eyes per day)*
At or prior to admission	245	25	10·2	—
Up to acute eye surgery or discharge; mean 5·2 days	220	9	4·1	0·79
Between acute eye surgery and fellow eye surgery or discharge; mean 6·7 days	187	14	7·5	1·12
0–1 month after discharge	52	7	13·4	0·48
1–12 months after discharge	35	2	5·7	0·02
12–48 months after discharge (mean 26 months)	14	1	7·1	0·02

before it could be treated surgically. Forty-eight patients (19·5%) developed acute ACG in the fellow eye either by the time they were admitted or during their stay in hospital. Ten patients developed acute ACG following discharge from hospital (7 of these during the first month after discharge). Twenty-nine of the 52 patients discharged from hospital without surgery to the fellow eye did eventually undergo surgery to that eye, 10 following an attack of acute ACG and 19 electively.

Timing of attacks. The timing of fellow eye ACG attacks is detailed in Table 2. Twenty-five patients (10·2%) had bilateral acute ACG on admission, and 7 of these were induced by a mydriatic. Of the remaining 220 patients 9 developed acute ACG in the fellow eye prior to surgery on the first eye, and 14 more developed similar attacks in the early postoperative period. The greatest susceptibility to acute ACG in the fellow eye is from the time of admission up to the first month after discharge, the first postoperative week being the most critical period. This increased susceptibility is illustrated by the high number of attacks per 100 eyes per day (attack rate) during this period.

Table 3 *Effect of treatment on the incidence of acute ACG in the fellow eye prior to initial surgery (mean 5·2 days)*

Regimen of treatment	*No. of eyes studied*	*No. developing acute ACG*	*Percent*	*Attack rate (no. of attacks per 100 eyes per day)*
CA inhib+pilo*	56	1	1·8	0·35
Pilo 2% or stronger 4 times a day	63	2	3·2	0·62
Other pilo regimen	91	4	4·3	0·83
No treatment	10	2	20·0	3·85
Total	220	9	4·1	0·79

*CA Inhib=carbonic anhydrase inhibitors. Pilo=pilocarpine drops.

Table 4 *Effect of treatment on the incidence of acute ACG between first eye surgery and fellow eye surgery or discharge (mean 6·7 days)*

Regimen of treatment	*No. of eyes studied*	*No. developing acute ACG*	*Percent*	*Attack rate (no. of attacks per 100 eyes per day)*
Pilo* fellow eye, no mydriatic† operated eye	16	0	0	0
Pilo 2% or stronger 4 times a day fellow eye, mydriatic operated eye	49	2	4·1	0·61
Other pilo regimen fellow eye, mydriatic operated eye	111	7	6·3	0·94
No pilo fellow eye, mydriatic operated eye	11	5	45·0	6·72
Total	187	14	7·5	1·12

*Pilo=pilocarpine drops.

†Mydriatics prescribed included 2% homatropine, 1% atropine, 1% cyclopentolate, 10% phenylephrine. These were all associated with at least one acute ACG attack in a fellow eye.

Patient's general condition. General systemic disorders did not appear to have any predisposing effect, but drugs with anticholinergic effects may have been a factor. The numbers, however, were too small to draw definite conclusions.

OPHTHALMIC TREATMENT

Preoperatively (Table 3). In the interval between admission and surgery to the first eye patients who received carbonic anhydrase inhibitors (in this sample acetazolamide 250 mg 2 to 4 times a day) plus pilocarpine drops to both eyes appeared less liable to develop acute ACG in the fellow eye, but there was one exception. Two of the 10 fellow eyes receiving no treatment developed acute ACG, representing an attack rate of 3·85 attacks per 100 eyes per day. If the fellow eye received pilocarpine drops, the risk of an acute attack appeared to be less.

Early postoperative period (Table 4). Fourteen attacks occurred during the period between surgery to the acute eye and surgery to the fellow eye, or discharge without surgery. Of these, 4 occurred on the first postoperative day. All these patients had had general anaesthesia, and apart from intramuscular atropine premedication there was no other common factor in their management.

In relation to postoperative medication, the results in Table 4 show a much higher incidence of acute ACG in the fellow eye when mydriatics had been prescribed for the operated eye and no prophylaxis for the fellow eye. Conversely no acute ACG occurred in fellow eyes if mydriatics were not used on the operated eye.

First month of follow-up (Table 5). Seven out of 52 fellow eyes developed acute ACG during this period, and these were confined to the 38 patients receiving mydriatic in the operated eye. None of the 14 patients receiving no mydriatic to the operated eye developed acute ACG (all patients were on pilocarpine to the fellow eye).

Subsequent follow-up. Once unoperated eyes had been followed up for more than one month, and mydriatic drops to the operated eye had been stopped, the liability to an acute ACG attack became less (Table 1). Nonetheless, attacks did occur up to 4 years after initial admission.

Discussion

The sample of patients studied is representative of patients presenting with acute ACG. The 2:1 female preponderance and the mean age in the mid 60s is consistent with the many previous studies of this condition. The findings of this study confirm Lowe's observation[5] that no medical regimen guarantees freedom from an attack of acute ACG in the fellow eye.

INCIDENCE AND TIMING OF FELLOW EYE ATTACKS

Acute ACG in the fellow eye occurs most frequently during the period between the initial onset of symptoms in the acute eye and the end of the first month of out patient follow up. Table 2 illustrates this tendency to early involvement of the fellow eye. Eighteen attacks occurred on or prior to admission without being provoked by mydriatics, and a further 9 occurred in hospital before any surgery was performed or any mydriatic treatment prescribed. Twenty-seven fellow eyes (11% total) therefore developed acute ACG early without mydriatic being implicated. However, 7 patients presented with bilateral acute ACG induced by mydriatics, and postoperative treatment with mydriatics to the acute eye resulted in a higher incidence of acute ACG in unoperated fellow eyes when not protected by miotics. This emphasises the bilateral nature of the condition, but also that the use of mydriatics to the operated eye constitutes an additional risk factor.

MANAGEMENT OF THE FELLOW EYE

Many studies, including recent series by Snow[6] and Playfair and Watson,[7] have emphasised the value of prophylactic peripheral iridectomy for the fellow eye.

As regards the timing of this procedure, the results of this study would favour bilateral simultaneous surgery on the acute and the fellow eye as the only means of avoiding acute ACG occurring in the fellow eye postoperatively. The principal arguments against

Table 5 *Effect of treatment on incidence of acute ACG in the fellow eye in first month after discharge*

Regimen of treatment	*No. of eyes studied*	*No. developing acute ACG*	*Percent*	*Attack rate (no. of attacks per 100 eyes per day)*
Pilo fellow eye, no mydriatic operated eye	14	0	0	0
Pilo 2% or stronger 4 times a day fellow eye, mydriatic operated eye	14	3	21·4	0·76
Other pilo regimens fellow eye, mydriatic operated eye	24	4	16·7	0·60
Total	52	7	13·4	0·48

this would be the risk of endophthalmitis or malignant glaucoma occurring bilaterally. However, none of the 51 patients submitted to simultaneous bilateral surgery had either of these complications; nor did they occur in any of the patients treated surgically on separate occasions.

However, in view of the possible disastrous consequences of malignant glaucoma or endophthalmitis occurring bilaterally, however infrequently, some surgeons would still prefer not to perform bilateral simultaneous surgery on the acute and the fellow eye, and surgery on the fellow eye is occasionally postponed for various reasons. Therefore the question remains how best to treat the fellow eye until this is performed. Carbonic anhydrase inhibitors do appear to have a weak protective effect, and this would be consistent with their established place in the initial treatment of acute ACG.

Pilocarpine appears to have a protective effect when compared with no prophylactic treatment, especially if a mydriatic is used in the operated eye. Aqueous pilocarpine is effective only for 6 hours whatever its strength, so a frequency of instillation of 4 times a day would be logical. However, no individual pilocarpine regimen conferred a significantly greater protective effect in this series.

An increased risk to the fellow eye is caused by the instillation of mydriatic in the operated eye. This was true whether the patient was in hospital or at home. It is unlikely that enough topically applied mydriatic is absorbed systemically to cause an attack of acute ACG in the fellow eye, and it is more likely that mydriatic is either mistakenly applied to the fellow eye or is inadvertently transferred to the fellow eye by rubbing both eyes in turn. The acute eye often requires mydriatic treatment postoperatively, and, as this puts the fellow eye at risk from acute ACG, surgery to that eye should be performed as soon as possible. If the patient has to go home prior to prophylactic surgery, mydriatics in the operated eye should be avoided where possible.

CONCLUSIONS

Acute primary ACG is potentially a bilateral condition with early involvement of the second eye being frequent. In these patients the fellow eye will be at risk from a similar attack no matter what medical treatment is given. There is a high incidence of acute ACG in the fellow eye when the patient is in hospital, and the risk is further increased by mydriatic treatment to the operated eye, particularly if the fellow eye is not protected by pilocarpine. Prophylactic peripheral iridectomy on the fellow eye should be done either simultaneously or within a few days of surgery on the acute eye, and it is not advisable to send the patient home or postpone surgery longer than is absolutely necessary. During the interval before surgery to the fellow eye pilocarpine drops instilled 6 hourly appear to be the safest treatment, and supplementary acetazolamide 250 mg 2 to 4 times a day may possibly confer additional protection.

I thank the consultant surgeons of the Birmingham and Midland Eye Hospital for permission to study their patients, and Miss Eagling and Mr O'Neill for their helpful advice and encouragement.

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British Journal of Ophthalmology, 1982, **66**, 580–582

Prevalence of trachoma among children in East Jerusalem in 1980

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SUMMARY In an ophthalmic survey conducted in East Jerusalem during 1980 comprising 8896 nursery and primary school children aged 3 to 12 years not a single case of active trachoma could be detected. A similar study carried out in 1968, encompassing the same geographical area, revealed a prevalence of 6·4% among the school children and of 12·5% among the nursery school infants, while a subsequent survey performed in 1971, including the same population age group, showed a sharp decrease in the incidence of trachoma to a level as low as 1%. This gradual and continuous decline in the prevalence of the disease towards its end point of apparent eradication was preceded by a marked improvement in the socioeconomic status and personal and public hygiene of the general population.

Endemic trachoma constitutes a major public health threat and is the chief cause of visual impairment and preventable blindness in certain developing countries. In fact this disease still remains a universal problem.[1] Despite the immense efforts invested in its eradication about 400 to 500 million individuals are afflicted with it.[2] One of the major areas of the world where trachoma is as yet undefeated is the Middle East.[3–5]

Epidemiological studies have recorded a prevalence of 36% among the young population in certain parts of Saudi Arabia[6] and of 60·1% in Abu-Dhabi.[7] In 1922 active trachoma was prevalent in 72% of the Arab school children throughout Palestine, while in 1939 this incidence had decreased to 49%.[8] In 1968, during an ophthalmic survey in East Jerusalem, trachoma was found in 12·5% of nursery school infants and in 6·4% of primary school children.[9] At this time an antitrachoma campaign was started, including treatment with antibiotic eye ointments. A subsequent study performed in 1971 including the same primary and nursery schools showed an incidence of only about 1% in this population group.[9]

In view of recent improvements in social and medical conditions an additional epidemiological study, applying the same basic clinical designs and encompassing the nursery and primary schools of the previous 2 surveys conducted by Maythar in 1968 and 1971, was undertaken to assess the current frequency and trend of trachoma.

Subjects and methods

Of the 26 governmental primary and nursery schools in East Jerusalem and environs 24 randomly chosen schools, with an attendance of 9364 pupils aged between 3 and 12 years, form the basis of this report. The eyes were examined with the aid of a 2 times magnifying loupe under proper illumination. The eyelids, the cornea, the corneoscleral limbus, and the bulbar, tarsal, and forniceal conjunctiva were thoroughly checked. Exploration of the last was achieved by flipping up the upper eyelid with 2 fingers while the child was looking down and at the same time exerting pressure on the globe from below, thus causing protrusion of the forniceal conjunctiva, where the follicles of trachoma usually appear first.

The criteria for the diagnosis and classification of the disease were based on the scoring system established by the WHO Expert Committee[10] and the WHO Fourth Scientific Group[11] and modified by us (Table 1). Patients with suspected trachoma, screened out during the examination, underwent slit-lamp biomicroscopy assessment and conjunctival scraping. The smears were Giemsa stained and tested for the presence of inclusion bodies. This latter method has remained the easiest technique available, and is a

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Table 1 *Criteria for classification and diagnosis of trachoma*

Clinical ocular findings	*Scoring*				
	0	*1*	*2*	*3*	*4*
Conjunctival hyperaemia	Absent	Mild	Moderate	Severe	Haemorrhagic
Conjunctival follicles	Absent	<5	5–10	11–15	>15
Conjunctival papillae	Absent	Minimal	Moderate	Pronounced	—
Corneal infiltrate	Absent	<1·5 Thickened cornea	>1·5 Thickened cornea	—	—
Pannus	Absent	<1 mm in the cornea	1–1·5 mm in the cornea	>1·5 mm in the cornea	—
Herbert's pits	Absent	1–3	>3	Entire upper lunula involved	Cornea encircled
Conjunctival scar	Absent	Mild	Moderate	Severe	Trichiasis and/or entropion

widely accepted mode for epidemiological screening for trachoma.[12]

Results

Of a total of 9364 pupils attending the schools included in the survey 8896 participated in the study and were screened for trachoma. On initial examination only 3 children displayed follicular infiltrate of the upper palpebral and forniceal conjunctiva in both eyes which, in spite of normal corneas and limbi, was suggestive of active trachoma. Biomicroscopy and laboratory tests failed to confirm the diagnosis. In one of the children a bacterial infection was diagnosed and successfully treated with antibiotics. Examination for the presence of inclusion bodies performed in 37 additional children with clinical signs of follicular or papillary hypertrophy due to nonspecific or allergic conjunctivitis proved negative.

Discussion

In the present study, undertaken 10 years after the previous studies by Maythar,[9] and involving the same nursery and elementary schools as those of Maythar's survey, when 8896 of 9364 (95%) regularly attending pupils were examined, no cases of active trachoma could be detected. The absence of the 468 children on the screening days was due to a variety of reasons and does not represent parental noncompliance with the survey itself. Moreover the number of absentees compared with that of the examined children is too small to affect the results statistically ($p=0{\cdot}0003$).

The findings of the current survey unequivocally demonstrate that the incidence of trachoma has steadily declined, approaching zero, thus reaching the desired end point in the fight for eradication of the disease in the geographical area at issue. Considering the fact that no preventive medical treatment has been administered in the last decade—except a routine sanitary supervision—it is reasonable to assume that these satisfactory results are due to the constantly improving hygienic and socioeconomic conditions.

The third report of the WHO Expert Committee[10] listed the following environmental factors as influencing the frequency of trachoma: race, climate, insect vectors, population density, diet and nutrition, cultural and social customs, general economic level, extrinsic contacts, educational level, and the presence of other ocular or general diseases.

Among all these factors only the first 2 and the social customs have remained unchanged in East Jerusalem, while all other conditions enumerated above have been vastly improved. The marked progress in the socioeconomic conditions and educational levels have been conducive to a decrease in population density and as well as to the enhancement of the dietary and nutritional state. At the same time the tremendous decrease of insect vectors, which are mainly responsible for the extrinsic contact, has contributed to the abolition of ocular discharge transmitted by flies.[13] The present availability of running water in almost every home and school, as well as the diminished incidence of bacterial conjunctivitis, largely facilitated the defeat of trachoma.

We are greatly indebted to Professor I. C. Michaelson and Dr B. Maythar for their valuable guidance.

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Massive ocular astrocytoma in a congenitally deformed eye

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SUMMARY A large retinal astrocytoma filled all of the posterior chamber of the congenitally blind and deformed eye of a 26-year-old male. History, clinical findings, and pathological study with special stains allowed for an unusually complete presentation of this rare intraocular neoplasm.

Astrocytomas of the inner eye are rare neuroectodermal hamartomas.[1 2] They may originate in the retina[3] or in the optic nerve head.[4] Their advanced stages are usually found in the laboratory in eyes that were removed because of pain and blindness,[3] but in their early stages they may present to the clinician with all the signs of active intraocular tumour growth[1] and may be clinically indistinguishable from retinoblastoma.[2] Like other extracerebral gliomas in the head region intraocular astrocytomas typically are benign.[5] Gliomatous tumours in the eye present in a broad and continuous spectrum of space-taking processes showing excessive reactive gliosis on one end and active neoplastic glial growth on the other.[3] The reactive tumours are also known as massive gliosis and are relatively common. True intraocular gliomas are exceedingly rare. An attempt to find features that would allow for an exact separation of massive gliosis from the neoplastic types in a larger series has failed.[3] All these glial tumours occur in patients who show no signs of generalised phakomatoses, of course.

It is the purpose of this paper to present the case of a patient with an astrocytoma that completely filled a congenitally deformed eye and extended into the optic nerve head, and who had a slight congenital defect in the other eye.

Case report

This 26-year-old white male was first seen in March 1978 with a blind, painful, and unsightly left eye. The family history was negative, but it may be of interest that the patient was the fifth of 5 living siblings and that one sister died at the age of 1 month, while another sister was stillborn. The patient was born of a normal pregnancy, at full term by a normal delivery, and was not in an incubator. He is of good general health and stated that he had never been sick. He has no signs of neurofibromatosis or other generalised disease. The left eye was recognised as poorly developed at birth and it never had any vision. Throughout his childhood it did not bother the patient, but within the last 2 years it became painful and ugly.

Clinical examination revealed a vision of 20/20 and J O with a −4·00+0·50 axis 180° in the right eye. This eye had a normal visual field. Fundus examination of the right eye revealed a relatively large temporal conus of the disc, with an anomalous choroidal blood vessel crossing the region of the conus. The left eye was blind. It was irritable and also exhibited band keratopathy as well as dense corneal scarring, which prevented a view into deeper parts of the eye; it appeared to be small. In 1967 the eye had a low intraocular pressure. In 1976 an irregular staphyloma was noticed on the temporal side between 2 and 6 o'clock. At that time, the intraocular pressure was 28·0 mmHg by applanation tonometry. There was distinct rubeosis iridis. After the situation had been discussed with the patient he asked to have the eye removed. This was done on 22 March 1978 under general anaesthesia.

The eye measured 22×19×19 mm. The cornea was white and scar-like. There was an extensive staphyloma, with bluish discolouration of the sclera. Transillumination with the egg candler[6] showed the eye to be filled with a solid mass. When the eyeball was opened in a horizontal plane, the anterior chamber could be recognised and was partly filled with whitish exudate. The iris was continuous, and its front surface had a normal appearance. A white

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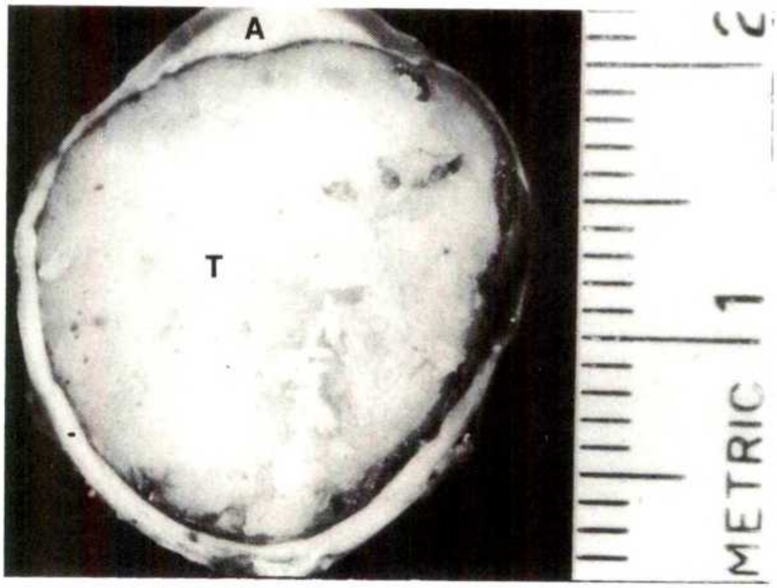

Fig. 1 *Gross view of the eye after sectioning. The anterior chamber* (A) *filled with a yellowish substance. The iris is visible. The inner eye behind the iris is totally filled with a white tumour* (T). *(×2·8).*

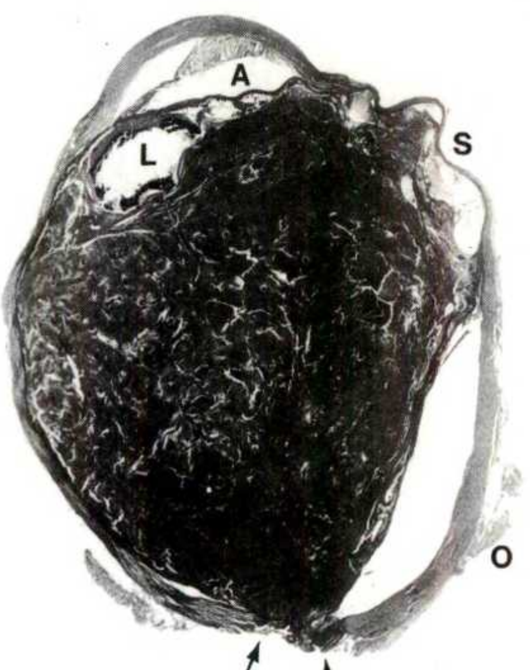

Fig. 2 *Cross-section of the eye showing exudate in the anterior chamber* (A), *the lens* (L) *with much of the lens substance broken out because of calcification, the staphyloma on the right (S), the tumour filling all of the inner eye behind the iris, and the hole in the sclera posteriorly (between arrows). The inferior oblique insertion is seen on the sclera* (O). *(Paraffin section, H and E stain, ×3·4).*

tumour of firm consistency filled the remainder of the eye (Fig. 1). In the place of the optic nerve the posterior sclera had a hole.

Microscopic study of paraffin sections (Fig. 2) revealed a continuous corneal epithelium of somewhat irregular thickness, with a dense fibrous pannus containing only a few patent blood vessels. Bowman's membrane was seen under the pannus in partly calcified fragments. The corneal stroma showed much scarring and some neovascularisation. The anterior chamber was shallow, and it was partly filled with serous exudate containing cholesterol crystal spaces and many histiocytes. Anterior peripheral synechiae closed the angle completely. The iris was atrophic and showed distinct neovascularisation, with relatively large vessels. The pupil was not recognised. A staphyloma was seen in the region of the ciliary body on one side (Fig. 2); the lens was pushed to the opposite side and was calcified. Tumour tissue filled the remainder of the inner eye. Parts of atrophic and distorted retina were seen in their normal place, but most of the retina was absent. The pigment epithelium had survived in some parts, but most of this layer had also degenerated and had formed a thin layer of bone overlying remnants of the choroid. The choroid was not directly involved with the tumour. Mononuclear cell infiltration was recognised, both diffusely and in a focal arrangement in the choroid. The optic nerve head was not seen, but the tumour extended through the hole cut during enucleation in the sclera in the place of the optic nerve (Fig. 2). The sclera was otherwise normal, though it had unusually large, long posterior ciliary nerves.

The tumour filling most of the inner eye had a

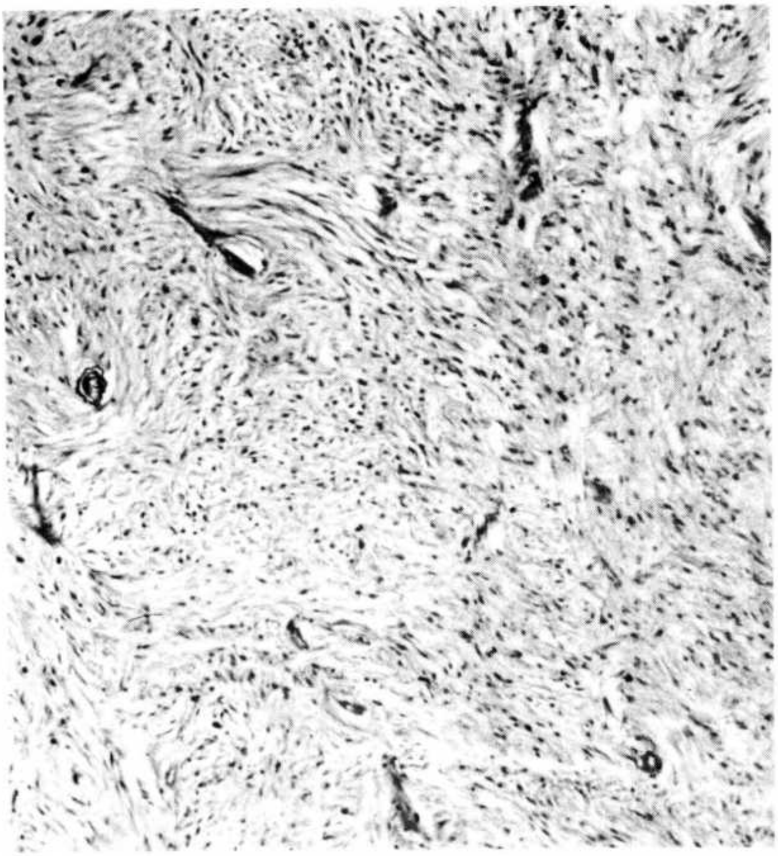

Fig. 3 *Tumour cells are arranged in interlacing bundles. They are quite uniform and exhibit ovoid or elongated nuclei. Numerous blood vessels with hyalinised walls are seen. (Thin paraffin section, H and E stain, ×300).*

slightly irregular appearance due to a poorly developed lobulated growth pattern. This was best visible at lower magnifications (Fig. 2). Higher power showed it to be composed of intertwining bundles of elongated bipolar cells with small and oval nuclei. All the cells appeared rather inactive, and no mitoses were found. Blood vessels were seen all through the tumour in a fairly regular distribution and their walls showed much hyalinisation (Fig. 3). Small areas of necrosis were found, and these showed early stages with necrotic preservation of portions of fibre bundles as well as later stages with hyalinisation and calcification. Phosphotungstic acid haematoxylin (PTAH) stain revealed fine and coarse neuroglial fibres in the tumour cells. Occasionally the cells were arranged radially around a small lumen to form rosettes (Fig. 4). Rosenthal fibres similar to those observed in pilocytic astrocytomas of the central nervous system were seen in places (Fig. 5). Reticulum stain showed only few reticulum fibres, which were associated with the blood vessels. The cytoplasm and the processes of the tumour cells failed to stain red with the Gomori trichrome stain. Electron microscopic examination of the formalin-fixed tissues showed numerous intracytoplasmic filaments. Unfortunately the preservation was not sufficient to allow for further identification of the cells and their filaments. However, the observations with special stains and light microscopy were sufficient to make the diagnosis of a retinal astrocytoma in this case.

Study of the posterior aspect of the enucleated eye with the scleral hole resulted in the impression that the astrocytoma was not completely removed. Thus on 15 May 1978 conjunctiva and Tenon's capsule were opened, the mesh implant was temporarily removed, and the optic nerve head was excised along with a 7 mm piece of the optic nerve stump. Histological study revealed additional astrocytoma on the lamina cribrosa, but the tumour had not extended into the nerve. The optic nerve was atrophic. The central retinal artery exhibited advanced narrowing due to an onion-layer-like proliferation of the endothelium (Fig. 6). The central retinal vein was large, but its lumen was filled with organised thrombus. Again, the ciliary nerves around the optic nerve were observed to be unusually large.

Discussion

Only a few well documented cases of retinal astrocytomas[2] and one case of astrocytoma of the optic nerve head[4] have been reported. The special value of the present case is in its history and some objective findings, which indicate its congenital nature. Associated with a slightly anomalous optic nerve head on the other side, the involved eye in the present case comes with a good history of being obviously abnormal and blind since birth. Unusually large ciliary nerves also indicate a primary neuroectodermal anomaly. However, study of the eye with its fully developed cornea, lens, sclera, choroid, portions of retina, and optic nerve indicates that it was relatively well developed before it became blind. The history, clinical observations, and pathological findings fit the picture of an eye that became involved with an intraocular tumour early in life—possibly before birth. This tumour slowly enlarged and filled the eye. It is impossible to say exactly where in the eye it originated, but the nasal displacement of the lens and the temporal staphyloma suggest the retinal periphery on the temporal side of the eye as a likely site of origin. The tumour was noninvasive, and thus it did not break the barriers of iris, Bruch's membrane, and lamina cribrosa. It caused posterior bulging of the lamina cribrosa, however. Its slow growth attracted most of the intraocular blood supply, and it caused atrophy of all other intraocular structures by compression and additional ischaemia. The ischaemia, finally, caused rubeosis, and the resulting secondary glaucoma led to pain and enucleation. The final stage, with rubeosis and secondary glaucoma, is common in cases with slowly growing intraocular tumours, of course.

As in all accepted cases of intraocular astrocytomas the tumour in the present case was not associated with any evidence of neurofibromatosis or another phakomatosis. The distinctly enlarged ciliary nerves,

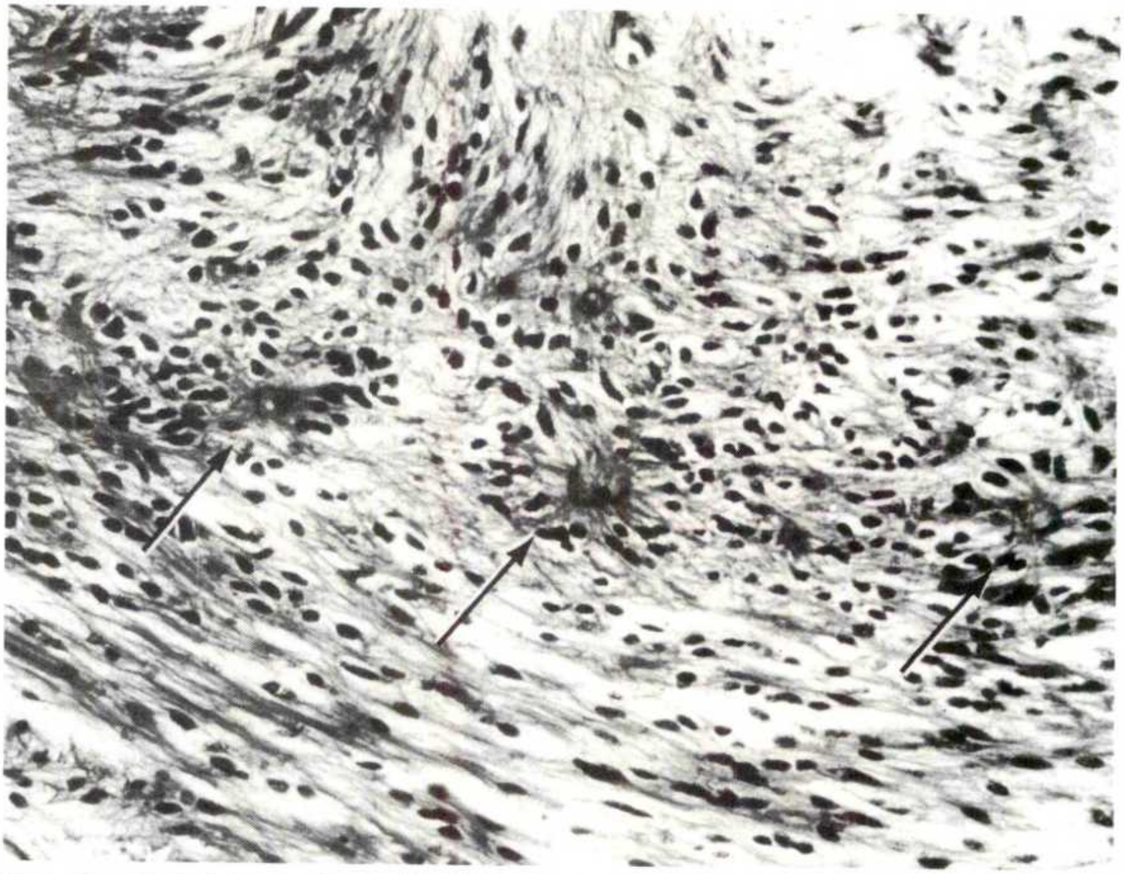

Fig. 4 *Occasionally the tumour cells assemble to form rosettes (arrows). Their nuclei are peripherally located and long cytoplasmic processes project to a central lumen. (Paraffin section, H and E stain, ×300).*

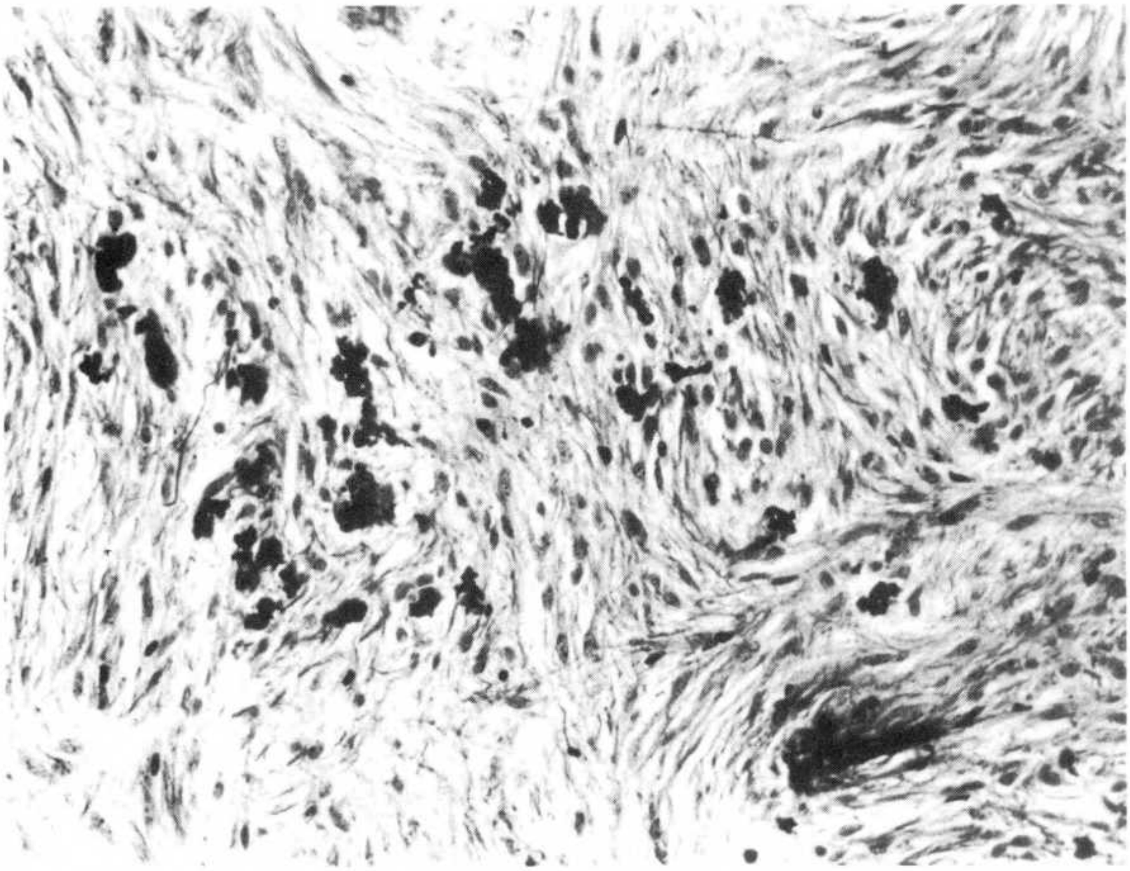

Fig. 5 *Darkly-stained Rosenthal fibres in cells of the present tumour. (Paraffin section, PTAH stain, ×300).*

however, are evidence of an overabundance of uveal nerves, which has been seen only as a congenital condition[7] and not as a reaction to chronic eye disease. This is found in some cases of choroidal melanoma—often part of associated overabundance of melanocytes and primitive ganglion cells and definitely related to so-called ocular melanosis. Uveal changes of this kind have been recognised as a congenital predisposition for the development of malignant uveal melanomas.[8 9] The significance of the large posterior ciliary nerves in the present case is not clear, but their presence is a sign of a congenital anomaly with excessive tissue of neuroectodermal origin. As in other hamartomas, the development of a retinal astrocytoma would probably originate in primitive glial elements left over from early development rather than from fully differentiated glial cells of the retina.[10]

The present case, thus, not only presents with an unusually advanced stage of an extremely rare and easily demonstrable intraocular tumour, but it also offers some indications that the tumour developed very early in life on the basis of a congenital anomaly. These facts are important additions to our knowledge not only of intraocular gliomas but also of principles concerning the nature and growth of ocular neoplasms in general.

This work was supported by the Research to Prevent Blindness Inc.

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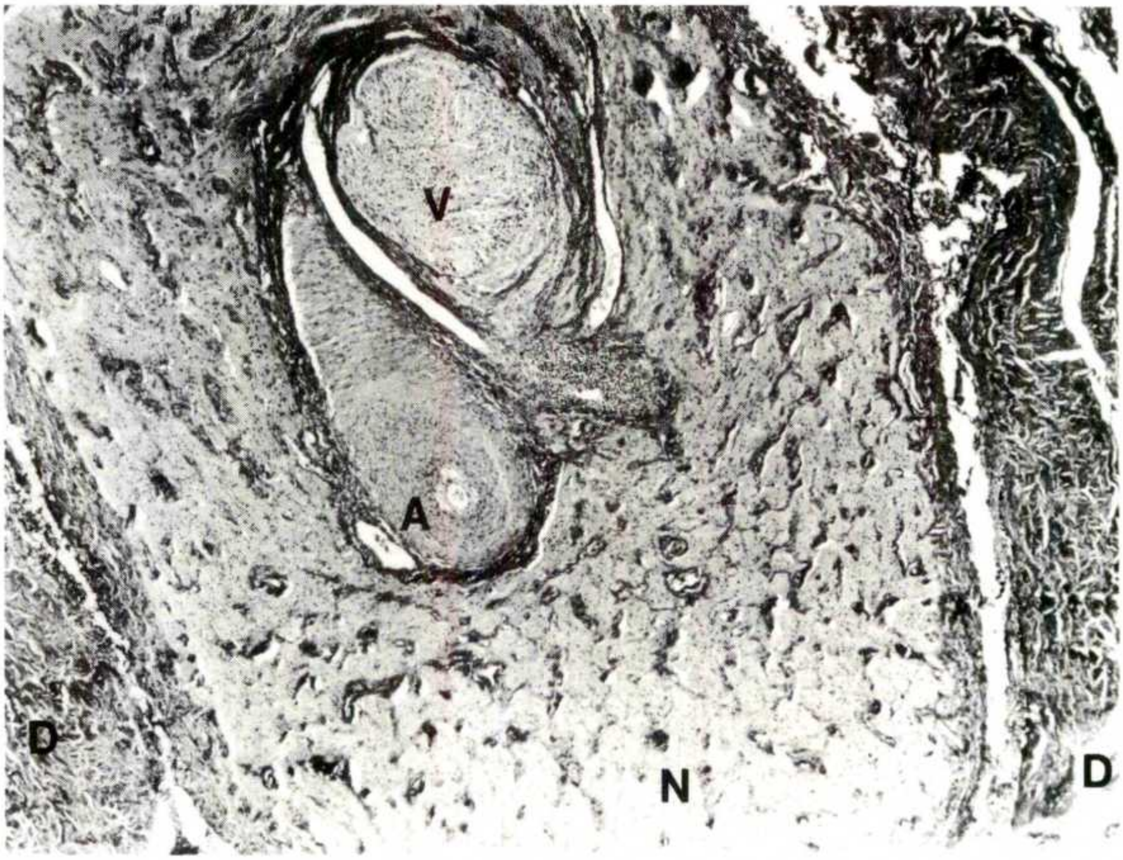

Fig. 6 *Cross-section of the atrophic optic nerve stump* (N) *with an extremely narrowed artery* (A) *and an organised thrombus in the central vein* (V). *No neoplasm is present at this level. The dura* (D) *is thickened. (Paraffin section, H and E stain, ×75).*

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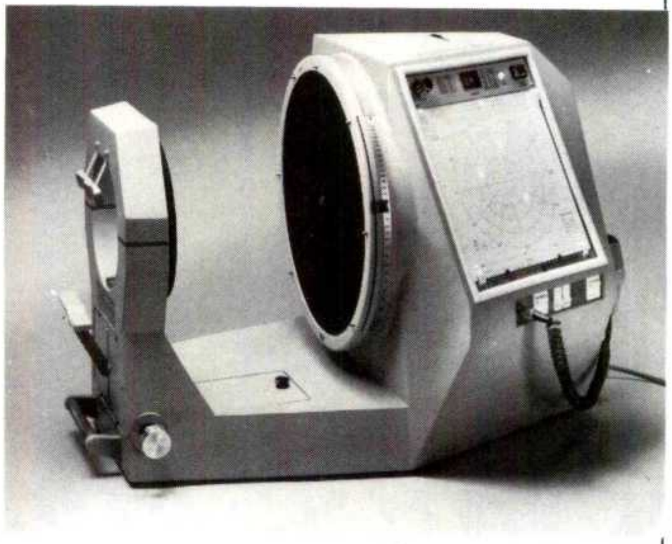

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British Journal of Ophthalmology, 1982, **66**, 589–593

Ophthalmomyiasis interna posterior: report of case caused by the reindeer warble fly larva and review of previous reported cases

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SUMMARY A 13-year-old boy from northern Norway had a living reindeer warble fly larva in the vitreous and typical subretinal tracks in his right eye. The larva was removed alive and normal visual acuity was preserved. This is the first time the reindeer warble fly larva (*Oedemagena tarandi*) has been found to cause myiasis in man.

Ophthalmomyiasis interna posterior (OIP) often produces an acute illness with inflammation, pain, and reduced visual acuity. In some cases, however, the disease may cause few or no symptoms, and the signs of OIP in the form of pigmented tracks in the fundus or a dead larva in the vitreous are accidentally discovered.[1–5]

We report the first case of OIP in which a larva was removed alive from the vitreous and the visual acuity of the eye was preserved. The larva was identified as a first-stage larva of the reindeer warble fly (*Oedemagena tarandi*). This fly has not previously been known to cause human myiasis.[6] A complete survey of the literature of OIP is presented.

Case report

At the end of September 1980 a 13-year-old boy from the coast of northern Norway presented with photophobia, vitreous floaters, and reduced visual acuity. For 4 weeks he had been treated with chloramphenicol eye drops for conjunctivitis. The right eye had a moderate anterior and posterior uveitis. A living larva, approximately 4·5×1 mm (Fig. 1), was seen in the vitreous. In the temporal part of the fundus multiple retinal haemorrhages were seen (Fig. 2) and also pigment epithelium disturbances forming curved lines (Fig. 3). The left eye was normal. Visual acuity RE 5/12, LE 5/5. Intraocular pressure RE 26 mmHg, LE 14 mmHg. The general physical examination was negative. There was no eosinophilia.

The anterior part of the eye gave no indication of where the larva had entered the eye. Treatment was with topical steroids, and on 7 October a pars plana vitrectomy was performed and the larva was freed from its vitreous connections. Through a separate pars plana opening the larva was removed alive with a

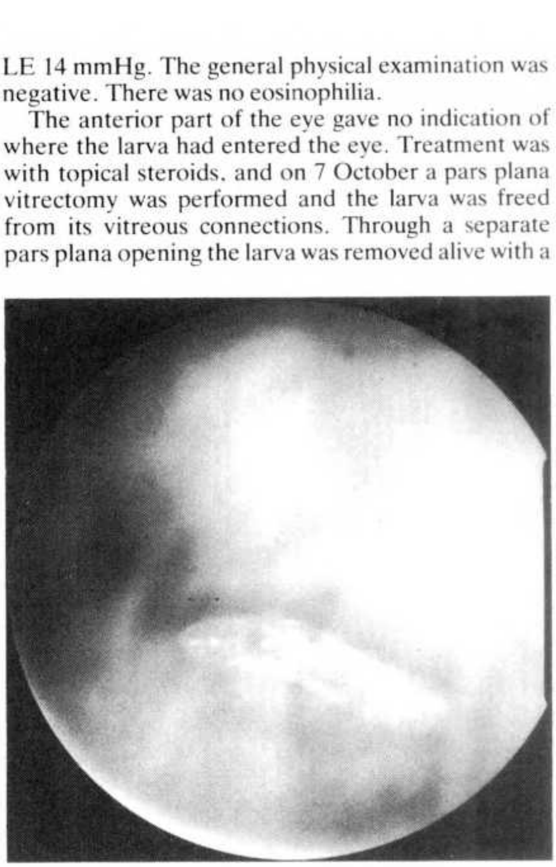

Fig. 1 *The reindeer warble fly larva in the vitreous.*

Correspondence to P. Syrdalen, MD, Department of Ophthalmology, Rikshospitalet, Oslo 1, Norway.

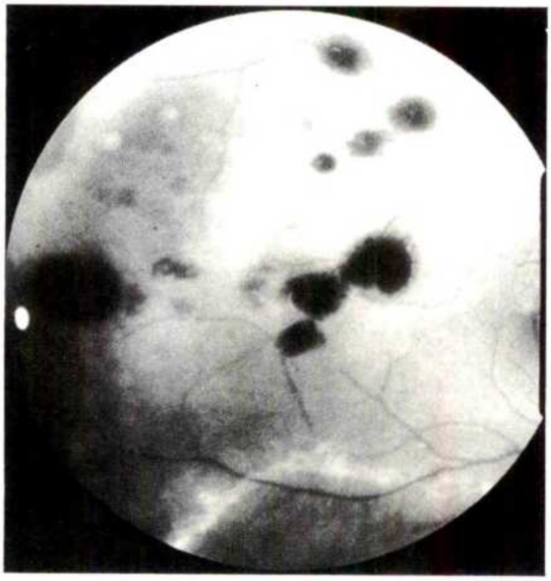

Fig. 2 *Retinal haemorrhages in the upper temporal quadrant.*

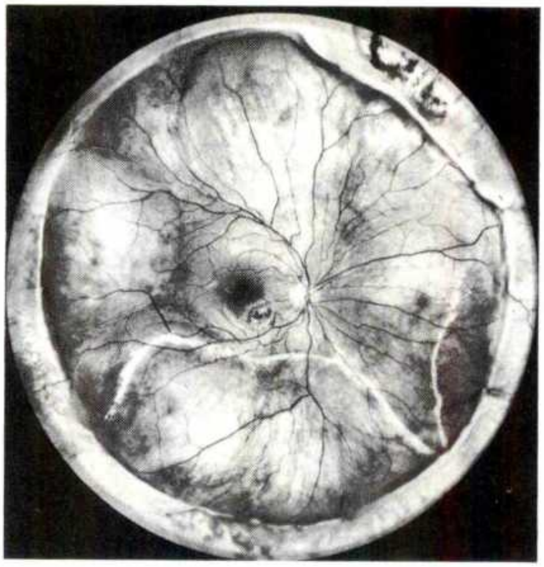

Fig. 3 *Composite postoperative picture showing the major part of the fundus and the cerclage. The pigmented track can be followed from 7 o'clock position to 5 o'clock position where a turn is made. The track gradually disappears at 2 o'clock. The round retinal hole, where it is believed that the larva penetrated into the vitreous, is in the middle of the pigmented scar on the local implant at 1 o'clock position. Below the macula the photocoagulation scar is seen.*

foreign body forceps. By grasping the larva lying on the fundus the forceps came into contact with retina, causing a small haemorrhage. This area was photocoagulated, because a retinal hole could not be excluded.

The operation was performed as a closed intraocular operation through the pars plana with corneal contact lens and operating microscope. During the operation it was noticed that the lens was subluxated with a defect in the zonular apparatus in the lower temporal quadrant. On 14 October a postoperative retinal detachment with a round equatorial hole at the 1 o'clock position was successfully operated on with a standard encircling procedure combined with extrascleral silicone rubber implant, cryosurgery, and drainage of subretinal fluid. At 7 months the visual acuity was RE 5/6. All retinal haemorrhages were now absorbed. Fig. 3 is a composite postoperative picture of the fundus taken 3 months after the operation.

THE LARVA

The cylindrical larva (Fig. 4) measured 4·5×0·9 mm. Superficially it resembled *Hypoderma lineatum* and *Hypoderma bovis*. The cephalopharyngeal skeleton, which is the most important feature for separating the first-stage larva of warble flies, agreed with the description given by Natvig,[7] Grunin,[8] and Zumpt,[9] of the first-stage larva of the reindeer warble fly (*Oedemagena tarandi*, order Diptera, family Oestridae). The specimen was also compared with material of *Oedemagena tarandi* and *Hypoderma lineatum*, collected by Natvig,[10] from the Zoological Museum in Oslo, confirming the identification.

LIFE HISTORY OF OEDEMAGENA TARANDI

The oviposition occurs mainly in July and August. The eggs are attached to the fine wooly down which constitutes the undercoat of the reindeer. The larva

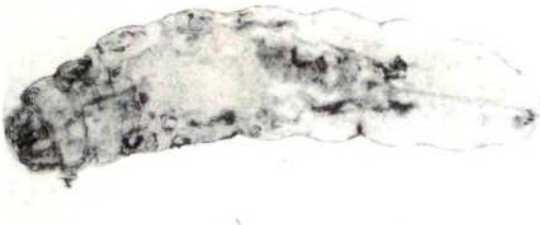

Fig. 4 *The extracted larva of the reindeer warble fly* (Oedemagena tarandi). *(×16).*

(0·7–0·8 mm) hatches after 4–7 days, penetrates the skin, and migrates in the connective tissue and the muscles towards the rump and spine of the host. The first larval stage lasts about 3 months, and the larva may reach a size of 9 mm. The larva moults its skin when it has ended its migration, becoming a second-stage larva. Small tumours, or warbles, appear when the larva first moults, mainly in October. The second and third larval stages last for 3–4 months each. The mature larva leaves the warble between April and July, falls to the ground, and pupates. The pupal stage lasts for 31–33 days and the new warble fly emerges.

REVIEW OF LITERATURE

In 1934 Anderson[11] referred to 8 previous cases of OIP and added a 9th case. Of these 9 eyes 6 were enucleated.

In a search of the literature after 1934 we have found an additional 19 reports[1–5,15–28] with a total of 22 cases (Table 1). Complete reports of 2 cases were not available (footnote, Table 1). As OIP we have listed all cases where a larva has been found behind the iris/lens diaphragm, or where characteristic tracks in the fundus have been seen. We have not included the case of Avizonis,[29] because the larva was not seen in the posterior part of the eye.

Of all the 31 reported cases a living larva has been observed in only 6 eyes[5,18,20,25,30,31] (information was missing for the cases of Forniches[15] and Biewers[17]). In one eye the larva died in the vitreous,[30] in one eye the living larva was removed from the vitreous by sclerotomy,[31] and in one eye the living larva was destroyed by vitrectomy.[26] Vision was lost in all these 3 cases. In one eye the larva was seen to move from the posterior to the anterior chamber, where it was removed.[18] In 2 eyes the living larva was subretinal,[5,25] and in one of these the larva was destroyed by photocoagulation.[25]

In 5 cases the larva died spontaneously without seriously damaging the eye[1,2,4,11,16] (information was missing for the case of Forniches[15]). We have had the opportunity to re-examine the patient described by Haarr.[16] After 38 years the remnants of the larva were still seen in the vitreous. The eye showed no sign of inflammation, and visual acuity was 5/5.

Of all 31 cases only one was bilateral,[5] and in only one eye has more than one larva been seen.[24]

Discussion

The reindeer warble fly is widely distributed over the range of its host in northern Eurasia and northern North America.[6] Except for one record of larvae in the skin of a musk ox (*Ovibus moscatus*) in Canada[12] the reindeer (*Rangifer tarandus*) has been the only animal known as host of the reindeer warble fly.[9] Until now the larva has been unknown as a human parasite,[6] though Natvig[13] observed that the fly often attacked and deposited eggs in the hair of humans. Brejev and Brejeva[14] tried to infect man with newly hatched larvae, without success. In our case the fly may have deposited eggs on the hair of the eyebrows or eyelids, and the hatched larvae then reached the eye on a short migration route.

Most authors have thought that the larva enters the eye through the ocular coats from the conjunctival sac. This view has been supported by histology.[32–34] In the present case it is possible that the larva penetrated the sclera in the 8 o'clock position just behind the ora where the pigmented track starts, wandered in the subretinal space, and penetrated the retina in the 1 o'clock position, making the round hole that caused the postoperative retinal detachment (Fig. 3).

Some authors have discussed the possibility of a haematogenous entry of the larva,[5,35] but proof of this has not yet been given. Byers and Kimura,[36] however, have reported haematogenous entry into the vitreous of a nematode.

In one case the larva entered the eye through the optic nerve head.[30] It has also been suggested that pigment lumps along the pigmented tracks in the fundus might represent spots where the larva has penetrated the eye.[3] This seems unlikely, because usually only one larva is present, and there may be several pigmented spots.[4,23] In a number of cases, haemorrhages in the fundus have been described.[5,11,19,24,25,28,30] They were also present in our case. Some authors believe that the haemorrhages could be explained by mechanical action of the larva.[25,28] In our case this is probably not true, as they had no connections with the pigmented tracks and no lesions in the retina could be seen. In our opinion these haemorrhages may be the result of a toxic, enzymatic, or immunological reaction caused by the larva. The larva seems to move easily between the retina and the pigment epithelium, making the pigmented tracks that are considered pathognomonic of OIP.[3–5,27,28] The larva may also wander in the choroid without producing any visible tracks.[5]

Lens dislocation has been reported in several cases of OIP,[16,18–20,26] including the present. This may be mechanical damage produced by the larva,[16,19] but the larva may also produce zonulolytic enzymes.[37,38]

A larva may wander between the anterior and posterior part of the eye,[18,19,23,24,29,35,39–41] and some authors consider the division between OIP and OIA (ophthalmomyiasis interna anterior) to be artificial.[19,42] However, the division between OIP and OIA is probably justified because of differences in diagnosis, treatment, and prognosis.[20,21]

As it is impossible to see subretinal tracks of a

Table 1 *Cases of ophthalmomyiasis interna posterior reported after 1934*

Year of publication	*Author*	*Country*	*Age/ Sex*	*Symptoms and findings*	*Treatment and result*
1943	Forniches don A*[15]	Spain	—	Larva found in the vitreous	*(Hypoderma bovis)*
1945	Haarr M[16]	Norway	12/M	Uveitis. Sublux. of lens. Dead larva in vitreous. No subretinal tracks	Conservative. Vision 5/5 at re-examination in 1981
1948	Biewers†[17]	Germany	10/F	Uveitis. Sublux. of lens	Enucleation *(Hypoderma bovis)*
1952	Vesely L[18]	Czechoslovakia	10/M	Sublux. of lens. Subretinal tracks. Uveitis. Vision hand movements. Larva seen to migrate from posterior to anterior chamber	Larva removed from anterior chamber *(Rhinoestrus purpureus)*. Vision 1/60
1954	Kiel E[19]	Germany	9/M	Uveitis. Sublux. of lens. Larva seen in vitreous. Retinal haemorrhages	Corticosteroids. Enucleation (Larva not found at necropsy)
1957	Eickemeyer KA[20]	Germany	11/M	Uveitis. Sublux. of lens. Living larva seen in vitreous	Enucleation. Larva found in ciliary body. *(Hypoderma bovis?)*
1958	Guadalupi U. Pampiglione S[21]	Italy	7/M	Uveitis. Larva not seen	Enucleation. Larva found in ciliary body. *(Hypoderma bovis)*
1958	Musial A[22]	Poland	15/F	Panophthalmia.	Enucleation. Larva found at necropsy
1969	Dixon JM *et al.*[23]	USA	45/F	Uveitis. Numerous winding trails in fundus. Larva moved from posterior to anterior chamber	Larva removed from anterior chamber. Vision 20/40 at 6 months follow-up. *(Cuterebra larva)*
1970	Hunt EW[1]	USA	43/F	Floater in the field of vision. No inflammation. Dead larva in the vitreous. Subretinal tracks	None. Vision 20/20 at 18 months follow-up
1970	Rakusin W[24]	S. Africa	29/F	Uveitis. Retinal oedema with haemorrhages. 2 larvae	Corticosteroids. Larvae removed, vision lost. (Probably *Oestrus ovis)*
1972	Brown JW[2]	USA	43/F	Disturbance of vision. Larva seen in the vitreous	Conservative
1974	Fitzgerald CR. Rubin ML[25]	USA	21/M	Anterior uveitis. Subretinal tracks. Larva seen to move subretinally. Retinal haemorrhages	Systemic prednisone and thiabendazole. Photocoagulation of larva. Vision 20/40 at 6 months follow-up
1976	Gass JDM. Lewis RA[3]	USA	19/M	Mild visual dimness. Subretinal tracks. No inflammation. Vision 6/6. No larva seen	
			15/F	Blurred vision. Subretinal tracks. No inflammation. Vision 6/12. No larva seen	None
			55/F	Subretinal tracks discovered by routine examination. Vision 6/6. No larva seen	
1977	Haut J *et al.*[26]	France	4/F	Uveitis. Sublux. of lens. Larva seen behind lens/iris diaphragm	Phacophagy, vitrectomy and subtotal retinectomy. Larva destroyed. Vision lost
1979	Slusher MM *et al.*[4]	USA	3	Subretinal tracks. Subretinal scar presumed to be a dead larva. No inflammation. Vision 20/25	None
			49/M	Floater in the field of vision. Dead larva in the vitreous. Subretinal tracks. Vision 20/200	
1979	Potgieter F. Scheuer JA[27]	S. Africa	12/M	Loss of vision. Uveitis. Subretinal tracks. No larva seen	Systemic corticosteroids. Vision 6/24 at 6 months follow-up
1980	Ziemianski MC *et al.*[28]	USA	15/M	Sudden loss of vision. No inflammation. Dead larva in vitreous. Subretinal tracks. Retinal haemorrhages. Vision: counting fingers at 1·5 m	Larva not removed. Photocoagulation of exit wound in retina
1981	Mason GI[5]	USA	33/M	Distortion in the central vision left eye. Bilateral subretinal tracks. Subretinal haemorrhages. A larva was seen to move subretinally in left eye. Vision RE 20/25, LE hand motions	Ultimate fate of larva unknown
1981	Syrdalen P *et al.*	Norway	13/M	Uveitis. Living larva in vitreous. Subretinal tracks. Retinal haemorrhages	Larva removed alive from vitreous *(Oedemagena tarandi)*. Vision 5/6 at 7 months follow-up

* Report not available. Case mentioned by Fernandez.[15]

† Report not available. Case mentioned by Eickemeyer.[20]

larva, the diagnosis of OIP may be very difficult. In a case of exudative uveitis and suspected foreign body, OIP should be considered.[42] In doubtful cases the determination of IgE in aquous humor and corresponding serum may help in the diagnosis.[37]

The treatment of OIP can be summarised as follows: a dead larva should not be removed if the eye is quiet.[3,28] A living larva in the vitreous should be removed if there is an inflammatory reaction which does not respond to steroid therapy.[3] If there is no inflammation, the larva can be watched inside the eye and developments followed.[3] If removal is considered, the pars plana technique probably offers the best chances of success. A living subretinal larva should be destroyed by photocoagulation if outside the macular area.[3,25,28] It may also be possible to kill the larva in the vitreous by photocoagulation, but this has not yet been done. To prevent retinal detachment an entry passage should be photocoagulated.[28] Steroids should be given according to the degree of inflammation.[3,27]

With the present means of diagnosis and treatment, the prognosis seems much more favourable today than at the beginning of the century.

Phototechnical assistance were given from Mr Jacques Lathion, University department for medical illustration and from Miss Else Morseth, Eye department, Rikshospitalet, Oslo.

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British Journal of Ophthalmology, 1982, **66**, 594–599

Periodic exophthalmos associated with the blue rubber bleb naevus syndrome: a case report

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SUMMARY A 71-year-old woman with the blue rubber bleb naevus syndrome experienced 4 episodes of self-limiting unilateral exophthalmos. It is suggested that a vascular malformation in the orbit is responsible for this phenomenon. A biopsy sample was taken of one of the cutaneous lesions and studied by light and transmission electron microscopy. The histological appearances are discussed in relation to possible mechanisms causing this periodic exophthalmos.

In 1958 Bean[1] gave the name 'blue rubber bleb naevus syndrome' to a condition characterised by erectile, bluish naevi of the skin associated with angiomatosis of the gastrointestinal tract. Since this classic description was published several reports have established that other systems may also have such vascular malformations. The lesions have been described in the nasopharynx,[2] liver,[3 4] lung,[3] pleura,[3 5] heart,[5] and central nervous system.[5] Recently a case of ocular involvement has been described, in which lesions were present in the conjunctiva, iris, and retina.[6]

We report a case of blue rubber bleb naevus syndrome associated with periodic exophthalmos, comment on this phenomenon, and describe the ultrastructure of one of the cutaenous lesions.

Case report

The patient, a 71-year-old female, presented to the Ophthalmology Department as an emergency with a history of having awakened that morning with a painful left eye. She had also noted that the vision in that eye was impaired.

On examination a marked degree of proptosis was present on the left side. This was measured with a Hertel exophthalmometer; the difference between the 2 sides was 9 mm (right 7 mm, left 16 mm). A complete ptosis was present on the left side. The lids could be opened only passively, with extreme difficulty, over the tense globe to reveal a chemotic conjunctiva. The eye movements on that side were grossly restricted. The corrected visual acuity was 6/9 in the right eye. An accurate visual acuity was unobtainable in the left eye owing to the ptosis and distressed state of the patient. The pupils were equal in size; however, an afferent pupil defect was present on the left side. Funduscopy revealed some congestion of the left retinal veins. Several lesions on the skin of face and neck were noted. The largest, present on the lobule of her right ear, measured 0·5 cm in diameter (Fig. 1). The lesions consisted of discrete, dark blue, easily compressible swellings

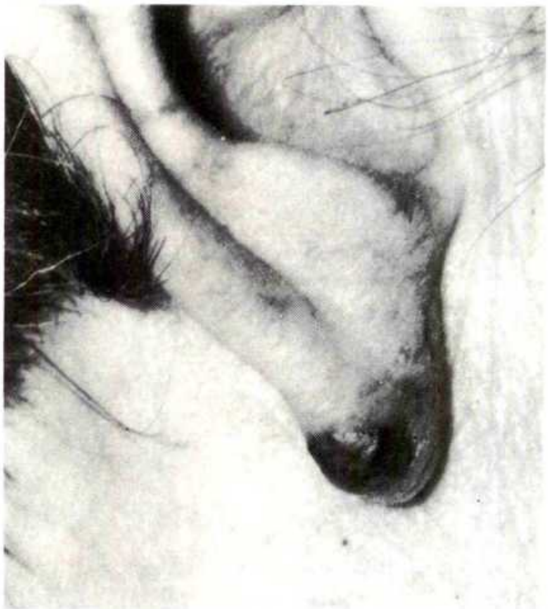

Fig. 1 *Blue rubber bleb naevus present on the lobule of right ear.*

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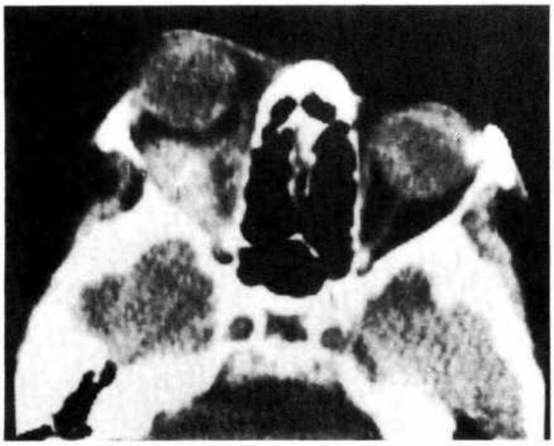


Fig. 2 *Computerised axial tomography of the orbits showing a high-density lesion in the left orbit separated from the globe by a narrow rim of fat. Note the marked degree of proptosis of the left eye.*

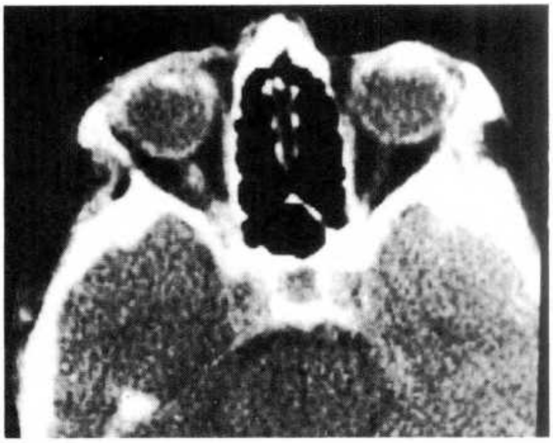


Fig. 4 *Computerised axial tomography of the orbits (with contrast enhancement) after the resolution of the second episode of proptosis. A small high-density lesion is present close to the left optic nerve.*

which had a bladder-like consistency. After the lesions were emptied on digital pressure they were seen to refill completely in a few seconds. Multiple haemangiomas were also present on the tongue and a few over the surface of the buccal mucosa. The patient stated that, although these lesions had been present for many years, they were not present in childhood. A large lesion on her lower lip bled profusely on one occasion, but had been treated successfully by radiotherapy 8 years earlier. Apart from this episode of bleeding there was no history of gastrointestinal haemorrhage.

Despite the absence of any subconjunctival haemorrhage, bleeding from or into an orbital vascular malformation was considered as the probable cause of the sudden proptosis. The patient was admitted for investigation. Computerised axial tomography of the orbits was performed. This revealed a high-density intraconal lesion, separated from the posterior surface of the globe by a narrow rim of fat (Fig. 2). At 2000 h, some 4 hours after the initial examination, the patient was re-examined. The ptosis was now incomplete and slight horizontal eye movements were now possible. In addition the patient noted that the pain was now less severe. In view of the improving physical signs a conservative approach was adopted, and the patient was treated with analgesics. The following morning both proptosis and ptosis had almost completely disappeared. Measurement of the proptosis revealed a clinically insignificant 2 mm disparity between the 2 sides. Slight diplopia was noted on the extremes of gaze, otherwise the eye movements had returned to normal. The corrected visual acuity in the left eye was now 6/9 part.

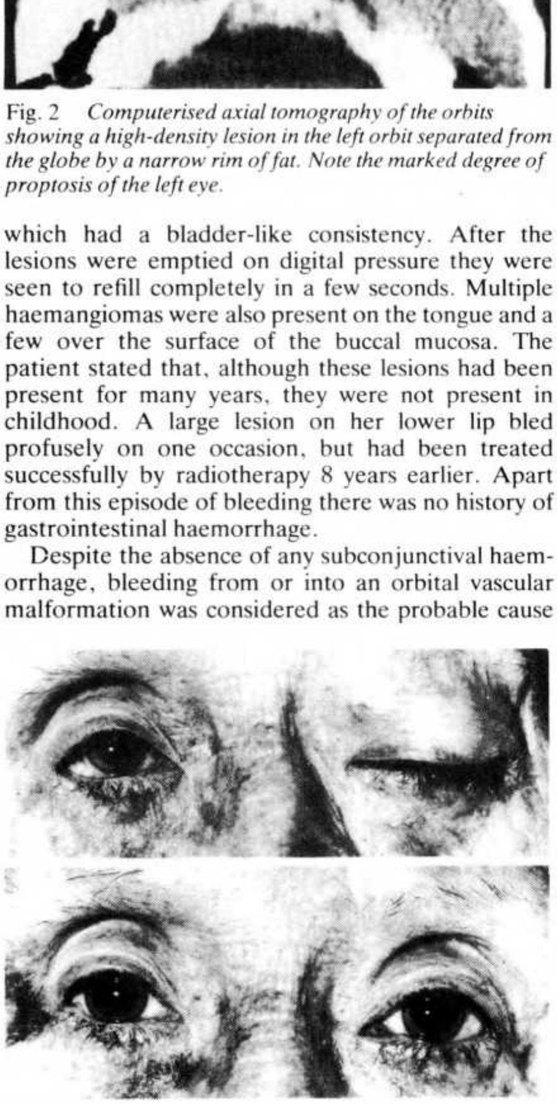


Fig. 3 *The appearance of the eyes:* (upper) *during an acute episode of exophthalmos;* (lower) *two days later.*

At 0400 h on the fourth day of admission the patient was awakened by a recurrence of the severe pain in her left eye. Examination revealed the same clinical picture seen on admission, the left eye was proptosed (the disparity measuring 8 mm), with a complete ptosis and external exophthalmoplegia (Fig. 3, upper). The patient was again treated only with analgesics. Computerised axial tomography of the orbits, this time with contrast enhancement, was performed later that day. Again the same high density lesion was present in the left orbit. The proptosis resolved over the next 48 hours (Fig. 3, lower).

On the seventh day after admission computerised axial tomography with enhancement was repeated; it revealed a small residual lesion in close relation to the optic nerve (Fig. 4).

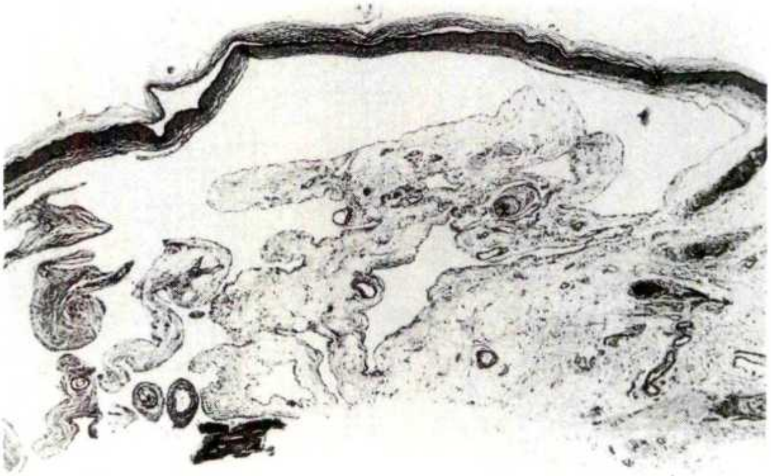
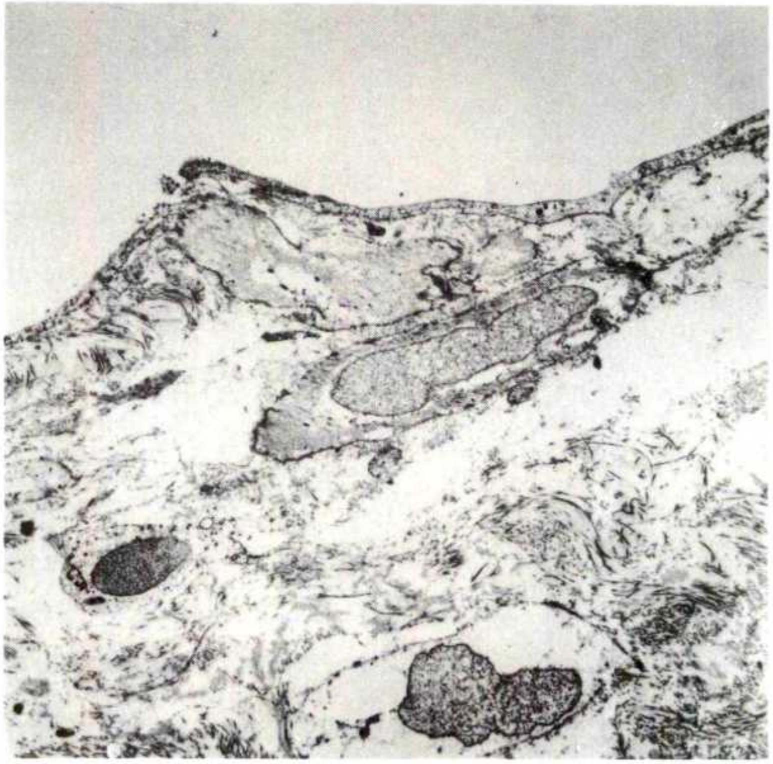


Fig. 5 *Light photomicrograph of the cutaneous lesion showing a benign haemangioma, the walls of which contain bundles of smooth muscle in some areas. (H and E, ×11·7).*

Further investigations, including full blood count, orbital venograms, and carotid angiography, were normal. Attempts to produce the proptosis by bending or straining were unsuccessful. The lesion on the right ear was biopsied under local anaesthesia. The patient remained asymptomatic and was discharged 12 days after admission.

Eight weeks later the patient returned to the department with a similar episode of painful proptosis of the left eye. Again the proptosis had been present on waking. The ocular findings were similar to the first admission, with a proptosed (8 mm difference between the 2 sides), and a chemotic eye. As in the previous admission a complete ptosis was present as well as a gross restriction in the eye movements. The corrected visual acuity in the



Figs 6a and 6b *Electron micrographs of 2 areas from the same cavernous channel. (× 3636).*

Fig. 6a *Smooth muscle cells lie immediately subjacent to the endothelium.*

affected eye was 6/12. On this occasion an afferent pupil defect was not noted. The patient was given sedatives and analgesics. The next morning the proptosis had resolved. She was discharged the following day, only to return 3 days later with similar symptoms. As on all the other occasions the proptosis had been present on waking. A similar regimen of sedation and analgesics was employed, with the now predictable resolution of symptoms by the following day. The patient was discharged 2 days later.

HISTOLOGICAL STUDIES

The cutaneous specimen was fixed in 10% formol saline for 24 hours and subsequently processed through graded alcohols to paraffin wax. Sections were cut at 4 μm and stained with haematoxylin and eosin, elastic Van Gieson, acid red direct yellow, and Martius scarlet blue for standard light microscopy.

Electron microscopy specimens were obtained from the paraffin block, and after removal of the wax, postfixed with osmium tetroxide and again dehydrated and embedded in epoxy resin. Sections were cut on an LKB ultratome at 0·5 μm, stained with toluidine blue, and examined with the light microscope for selection of appropriate areas. Subsequent ultrathin sections were cut at 80 nm, stained with lead citrate and uranyl acetate, and examined with an AEI Corinth electron microscope with an accelerating voltage of 60 Kv and magnifications ranging from 1200 to 20 000 diameters.

Light microscopy. The lesion from the ear lobule had the configuration of a benign cavernous haemangioma. The endothelial cells were low and attenuated. The stromal septa between the blood spaces varied; some comprised connective tissue, while others contained substantial smooth muscle components (Fig. 5).

Electron microscopy. The blood spaces were lined by a low pavemented endothelium, showing no exceptional features. The adjacent stroma reflected the picture seen on light microscopy. Fibroblasts and collagen bundles were the sole feature in some areas of the wall, while in other areas of the same blood space recognisable bundles of smooth muscle cells were present (Figs. 6a,b). Ultrastructurally these cells were more plump than the fibroblasts and contained orderly filaments related to dense bodies, both in the cytoplasm and at the plasma membrane. Abundant micropinocytotic vesicles were present, and a thin investing basement membrane was discernible. Collagen bundles were present adjacent to the smooth muscle cells lying immediately subjacent to the endothelium.

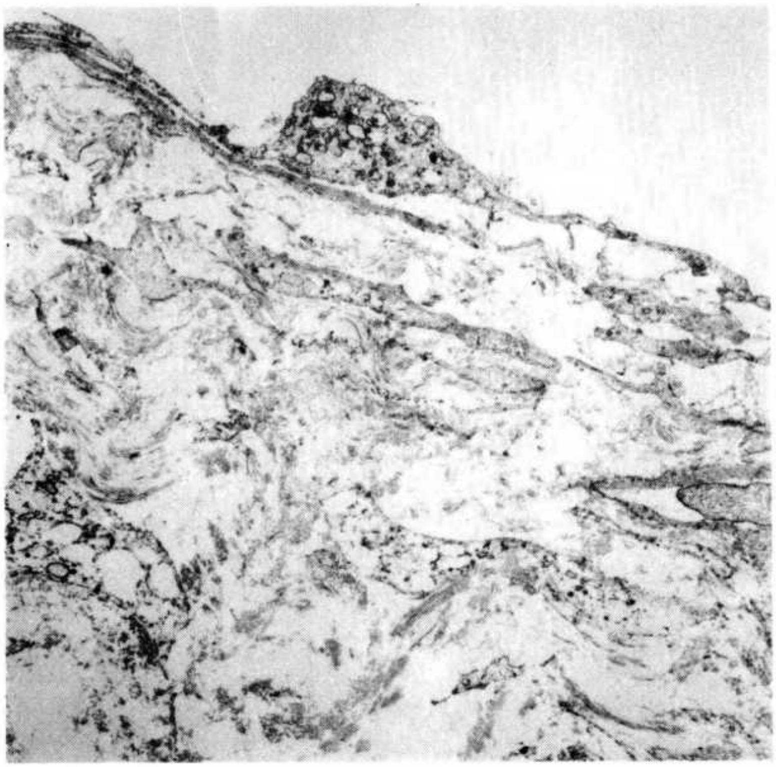


Fig. 6b *Fibroblasts and collagen constitute the vascular stroma.*

Discussion

Intermittent proptosis is a rare but well recognised clinical entity. Typically the clinical picture is that of a transient, unilateral proptosis of variable duration lasting from a few seconds to a few days, which may be precipitated by manoeuvres which increase the orbital venous pressure. The commonest cause of this condition is an orbital varix.[7] This may be a primary congenital venous malformation or secondary to an arteriovenous shunt.[8 9] The clinical picture presented by the patient in this report differs from the classical description of intermittent proptosis. A fundamental difference is the inability to produce the proptosis by increasing the orbital venous pressure. Furthermore normal orbital angiography and venography would suggest that the lesion is unlikely to be an orbital varix. We feel that the most likely cause for her periodic exophthalmos is the presence of an expansile vascular malformation in her orbit similar in nature to her cutaneous haemangiomas.

The lesion removed from the ear lobule in our patient was a benign cavernous haemangioma. The endothelial cells were attenuated throughout, unlike the cuboidal layer reported by Fine *et al.*[10] and claimed by those authors to be characteristic of the blue rubber bleb lesions. Rice and Fisher[3] reported that the dilated channels constituted an endothelial layer only, unlike our case, in which the walls of the blood spaces were composed of fibromuscular tissue, a feature emphasised by Bean[1] in his original description. The stromal component has received considerable attention, and from publications on these lesions 3 types emerge. Fretzin and Potter[2] observed fibrous walls, whereas Walshe *et al.*[11] observed muscular elements. Our case conformed most to that described by Fine *et al.*[10] in which both muscular and fibrous components are present. The ultrastructural evidence that we found shows clearly that smooth muscle cells and fibroblasts are applied closely to the endothelial spaces. They thus constitute a specific part of the vascular wall rather than an adjacent stromal component incorporated passively. It is interesting to note that both smooth muscle cells and fibroblasts are in evidence within the wall of the same vascular channel. A similar observation was made in a rather more complex lesion involving the brain.[12] As a result of their studies Rosenblum *et al.*[12] suggest that the blue rubber bleb lesion may encompass a wide variety of vascular malformation ranging from capillary telangiectasis to arteriovenous malformations.

It has been recognised previously that the cutaneous lesions of the blue rubber bleb naevus syndrome are capable of episodic swelling. Indeed our patient described an intermittent swelling of the lesions on her tongue and buccal mucosa. Episodic pain with or without an increase in size is also a feature of these lesions.[10 13] It is of interest to note that the pain associated with these lesions occurs typically at night. The exact mechanism for the variation in size of the lesions and the production of pain is unknown. Fine *et al.*[10] suggested that the pain is probably caused by contraction of the smooth muscle elements contained in the lesions.

Our studies on the ultrastructure of the cutaneous lesions confirm the presence of smooth muscle cells, closely related to the endothelial lining of the vascular channels. It is possible that segmental contraction of these smooth muscle elements in the distal aspect of the malformation could lead to dilatation of the proximal vascular channels and an increase in size of the lesion, and this mechanism may be responsible for at least the initial increase in size of the lesion. Once fully expanded, the orbital congestion produced would lead to local ischaemia and subsequent relaxation of the smooth muscle elements. An alternative explanation is that the vascular malformation is acting as ball valve, blocking the venous return from the orbit. Rowbottom and Little[14] described a case of haemangioma causing intermittent proptosis by compressing the venous drainage from the orbit at the superior orbital fissure. It is possible that both mechanisms may exist together.

The lesions of the blue rubber bleb naevus syndrome are often described as congenital or occurring in early childhood. However, this may not always be the case. Sakurane *et al.*[13] describe a case in which the cutaneous lesions developed between the ages of 19 and 23 years. Our patient was quite adamant that her lesions developed in adulthood and were not present in childhood.

We thank Mr A. J. Dark for allowing the publication of his clinical material and Mr T. Gray for his technical assistance.

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British Journal of Ophthalmology, 1982, **66**, 600–606

Apparent monoclonal origin of lymphocytes and plasma cells infiltrating ocular adnexal amyloid deposits: report of 2 cases

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SUMMARY Two cases of primary amyloidosis involving the orbit and lid respectively are described. Immunoperoxidase staining of the associated infiltrate of lymphocytes and plasma cells showed a clear preponderance of cells carrying λ light chains in one case and κ in the other. The predominant heavy chains were IgA and IgG respectively. It is suggested that these cases are 'burnt out' local plasmacytomas.

Although not common, amyloid infiltration of the lid and conjunctiva has been reported on many occasions. But similar involvement of the orbit is rare.[1] In most cases there is no history or evidence of any pre-existing local or systemic disease. Clinically the condition appears as a slowly progressive painless swelling involving lids or orbit.

The pathogenesis of the amyloid deposits remains obscure, but a consistent pathological feature is infiltration by lymphocytes, plasma cells, and foreign body giant cells.[2] Though these cells may represent a reaction to the deposition of amyloid, there is a strong possibility that the plasma cells may play a role in its deposition. This being so, the question arises whether or not they are 'neoplastic.' The boundary between orbital 'pseudotumours' in which amyloid is laid down and primary localised amyloidosis in which cellular infiltration is absent or minimal is not clear,[3] and a local plasmacytoma of the conjunctiva in which amyloid was later deposited has been reported.[4]

Identifying the immunoglobulins carried by lymphocytes and derived cells is of value in differentiating pseudotumours from lymphomas in that the former tend to have a heterogeneous population while the latter often show a predominance of cells carrying a particular light chain.[5–7] The present paper reports on the immunoglobulin labelling of cells associated with amyloid deposits in 2 cases in which the orbit and eyelid were respectively involved.

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Material and methods

CASES

1. A 78-year-old man presented with a 2-year history of a painless swelling in the right upper lid which was now causing ptosis to the extent of closing the eye. On examination a smooth hard mass was palpated in the right upper orbit; this protruded into the upper lid from behind and displaced the globe downwards. Right upward movement was limited. Right optic atrophy was noted. Orbital *x*-ray was normal, and CT scan showed no extension of the tumour behind the globe.

The patient had had a myocardial infarction 3 years previously and complained of shortness of breath but was otherwise well. Haemoglobin, white cell and platelet counts, and plasma urea and electrolyte levels were normal at this time.

At operation the tumour was poorly encapsulated and extended back over the globe for some distance. The tumour was therefore removed in a piecemeal manner. At follow-up a month after operation the lesion was thought to be returning: a firm mass, measuring approximately 1 cm in length was palpable under the orbital rim. The patient was lost to further follow-up.

2. A 46-year-old woman presented with thickening of the left lower lid resulting in entropion, which was subsequently corrected. Eighteen months later she was readmitted with recurrence of thickening of the left lateral canthus and tarsal plate for which a tarsal plate biopsy was performed.

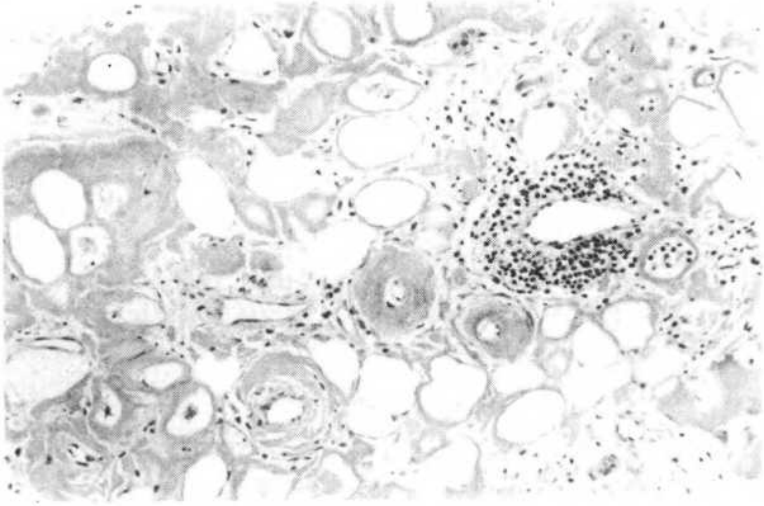

Fig. 1 Case 1. *Amyloid in adipose tissue and walls of small blood vessels and cuffing of a small blood vessel by lymphocytes. (PAS ×145).*

Subsequent investigations showed normal haematological indices and bone marrow. Immunoglobulin levels lay within the normal range and no paraprotein was present. Light chains were not detected in the urine. Chest *x*-ray was normal, and no evidence of myeloma was seen in the dorsal spine. She was otherwise well apart from recurrent urinary frequency and frequent ectopic beats.

METHODS

The tissue was fixed in unbuffered 10% formalin and embedded in ester wax for normal histology and paraffin wax for immunoperoxidase staining. Tissue for electron microscopy was postfixed in buffered glutaraldehyde (after recovery from the paraffin block in case 2). The PAP method[8] was used to demonstrate immunoglobulins. Rabbit antisera for human IgG, M, A, and D 150 types and κ and λ light chains were obtained from Dako except anti-IgE, which was supplied by Behring. The IgG and M antisera were diluted to 1/2000, the IgA, D, and E to 1/1000, and the anti-κ and λ to 1/3000. Most sections were counterstained by the sodium sulphate-alcian blue method for amyloid.[9] In case 1 sections were exposed to the antisera both with and without prior trypsinisation.

Results

CASE 1

Pathological appearances. The specimen consisted of 2 pieces of firm fibrofatty tissue measuring 3·0 cm×2·5 cm×1·5 cm and 2·5 cm×0·5 cm and a hard translucent nodule 1·3 cm×0·5 cm.

Microscopically the specimen consisted predominantly of structureless masses of eosinophilic material together with some fatty tissue and striated muscle. The hyaline material stained with Congo red and by the PAS method. It was birefringent and showed green dichroism after Congo red staining. Numerous foreign body giant cells were present, and there were foci of lymphocytic infiltration. Occasional plasma cells were identified in these foci, and there was cuffing of small blood vessels by lymphocytes.

The hyaline material was observed being laid down in rings in fatty tissue and also in striated muscle fibres (Fig. 1). A small area of bone formation was present (Fig. 2).

Electron microscopy. The hyaline material showed

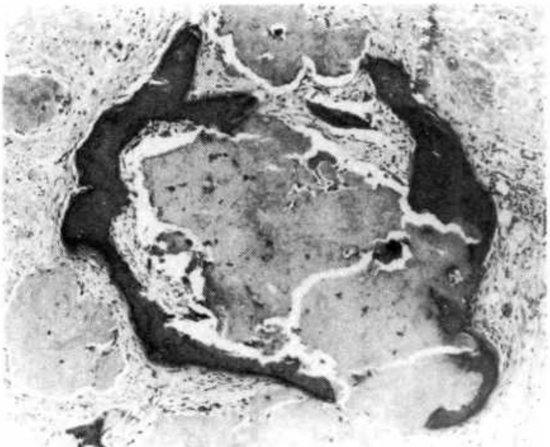

Fig. 2 Case 1. *Bone formation between masses of amyloid (H and E, ×54).*

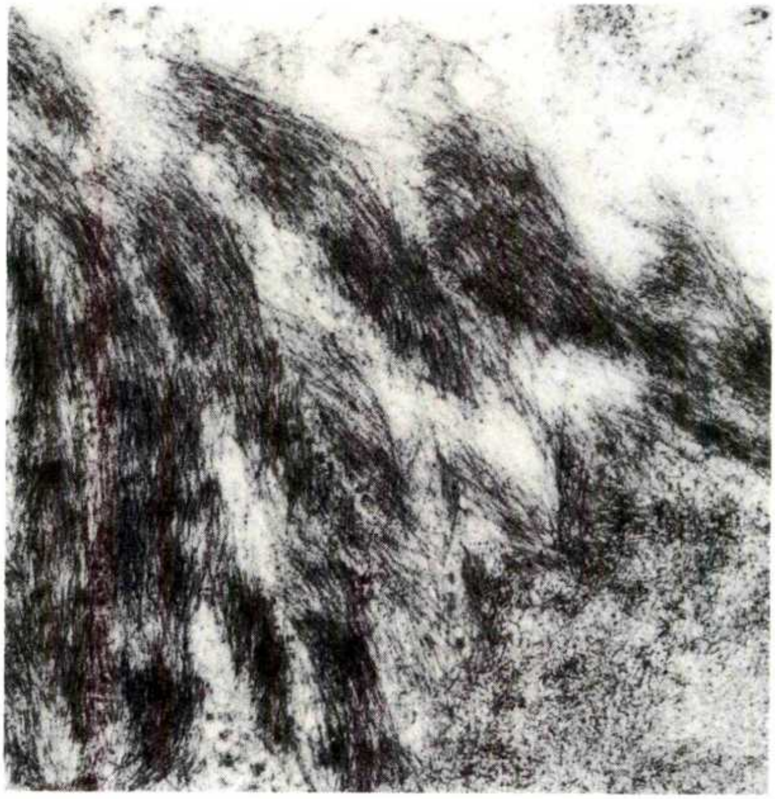

Fig. 3 Case 1. *Electron micrograph showing typical bundles of amyloid fibrils. (×38 000).*

interlacing bundles of non-branching fibrils typical of amyloid (Fig. 3).

Immunoperoxidase staining. Staining of substantial numbers of the lymphocytes and plasma cells occurred only with antisera for λ light chains (Fig. 4) and IgA. Labelled cells were not randomly distributed but tended to occur round the periphery of focal aggregates. It was therefore difficult to estimate the number stained with any accuracy, but in some aggregates it appeared to approach 50%. Only occasional cells stained with antisera for κ light chains (Fig. 5), IgG, IgM, IgE, or IgD. Prior treatment with trypsin appeared to increase the number of cells carrying IgA but otherwise did not affect the results significantly. Staining of the amyloid with or without prior trypsinisation was erratic. With anti-κ, λ, IgG, and IgM the larger masses were unstained except at their margins. Occasional small masses engulfed in giant cell cytoplasm were stained. Occasional giant cells also showed faint diffuse cytoplasmic staining with these antisera. The hyaline material was stained by the sodium-alcian blue counterstain.

CASE 2

Pathological appearances. The specimen consisted of an irregular strip of tissue, 1·5 cm×0·5 cm×0·4 cm.

Microscopically the tissue was composed of circumscribed masses of almost acellular hyaline material which stained positively by the PAS method and showed red-green dichroism with Congo red. Small arteries and arterioles in the vicinity also showed hyaline infiltration and mural thickening. A few foreign body giant cells were seen in relation to the material.

In the adjacent stroma was a mass of lymphocytes, plasma cells, and some histiocytes. Numerous Russell bodies and several small islands of hyaline material were present in the infiltrate (Figs. 6a,b). No epithelium was present in the specimen.

Electron microscopy. The hyaline material had the typical unbranched fibrillary structure of amyloid.

Immunoperoxidase staining. At the periphery of focal aggregates nearly 100% of the lymphocytes and plasma cells stained for the κ chain, though islands of unstained cells were present (Fig. 7). Somewhat

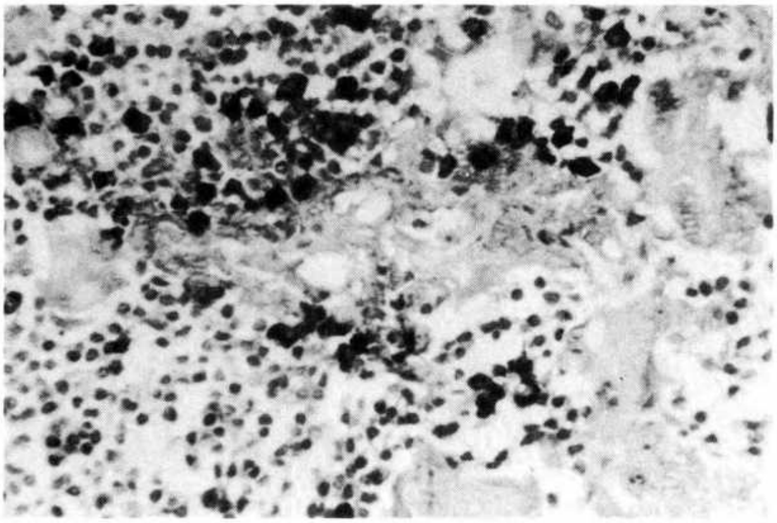

Fig. 4 Case 1.
Immunoperoxidase staining for λ light chains, substantial group of heavily stained cells. (×357).

fewer stained for IgG, and the staining was less dense (Fig. 8). Less than 1% of cells stained for the λ chain (Fig. 9), while occasional cells also stained for IgA and IgM. No cells stained for IgD and IgE.

The amyloid was generally unstained. Some giant cells showed weak staining with anti-λ and κ sera.

The hyaline material was stained by the sodium sulphate-alcian blue counterstain.

Discussion

By 1979, 14 cases of orbital amyloidosis had been published and these have been fully reviewed.[10] Since then a further 2 cases have appeared.[11 12] Computed tomographic scanning contributed to the diagnosis of these cases. The ages of the 16 cases ranged from 24 to 78, and 11 were females. Deposits of amyloid were not discovered elsewhere in these cases, but in a rather unusual case in a girl of 9[13] amyloidosis involved the inferior nasal meatus, the vocal cords, hard palate, and inner aspect of the nasal bridge, whence it extended into the upper and lower eyelids to the level of the orbital rims.

Amyloid (or hyaline) infiltration of the eyelid has been described and reviewed.[2 14–18] The cases appear to show a similar age and sex distribution to those arising in the orbit.

Deposits in ocular adnexal structures are very

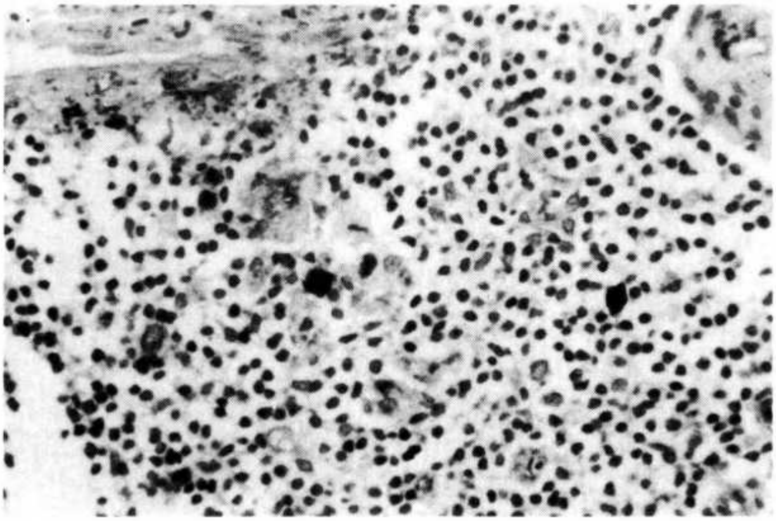

Fig. 5 Case 1.
Immunoperoxidase staining for κ light chains; only 2 positively stained cells in field comparable to that shown in Fig. 4. (×357).

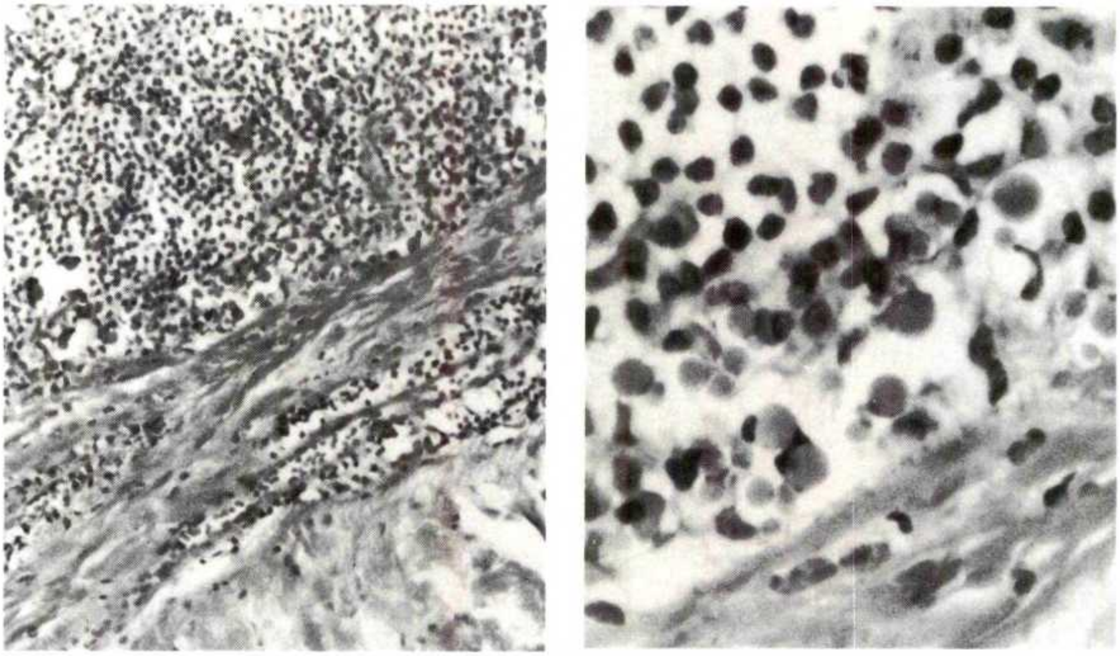
6a 6b

Fig. 6 Case 2. (a) *Heavy infiltrate of lymphocytes and plasma cells separated from mass of amyloid by fibrous band. (×178).* (b) *Same field, numerous Russell bodies mainly along fibrous band. (×750).*

uncommon in systemic amyloidosis.[18] By contrast deposits in the central retinal artery and vitreous body are more often seen in association with systemic amyloidosis than in its absence.[19]

The principal pathological features are similar whatever the location of the adnexal deposits. There is deposition of amyloid both as large masses and in the walls of small blood vessels and in adipose tissue. Giant cells are present in varying numbers, and a cellular infiltrate composed of lymphocytes and plasma cells is usually present, though its density may vary considerably and is sometimes minimal.[12] The 2 cases described here show these general features but differ in minor particulars. In case 1 the giant cell

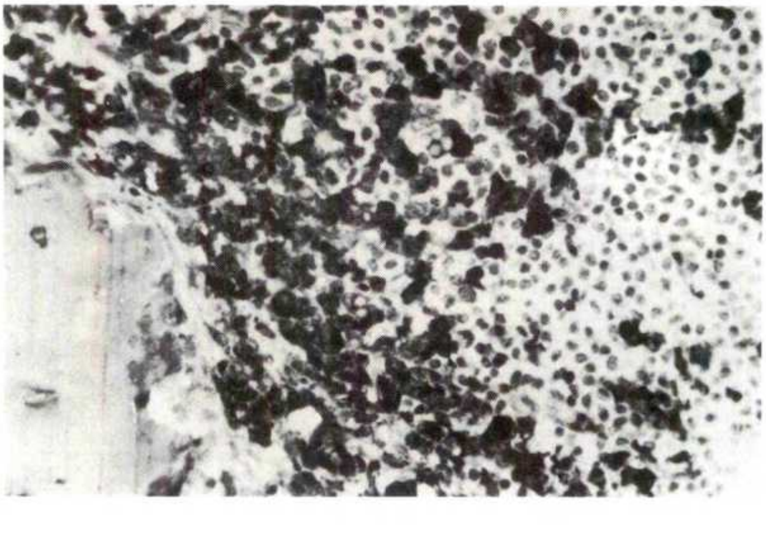

Fig. 7 Case 2. *Immunoperoxidase staining for κ light chains, substantial group of heavily stained cells at periphery of a lymphoid focus. (×357).*

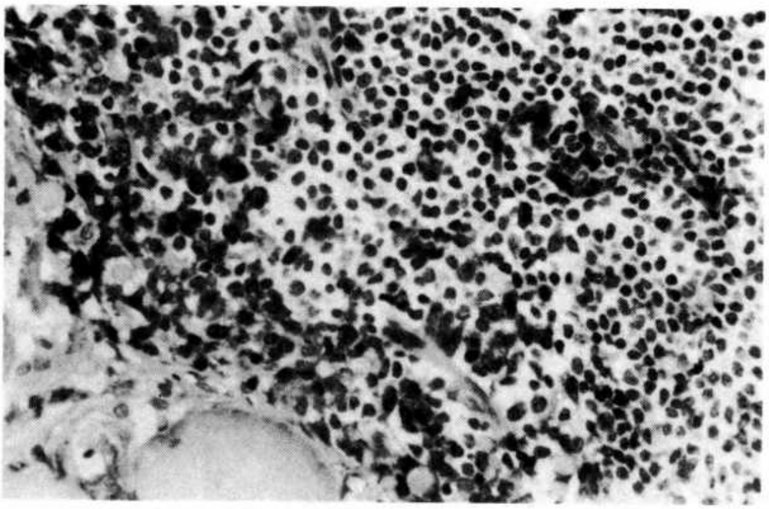

Fig. 8 Case 2. *Immunoperoxidase staining for IgG, substantial group of cells showing positive staining mainly at periphery of lymphoid focus. (×357).*

reaction is particularly conspicuous; the cellular infiltration is predominantly lymphocytic and not very dense. Bone formation is unusual, but has been described previously.[20] In case 2 the giant cell reaction was minimal and the cellular infiltrate denser and predominantly plasmacytic. The very numerous Russell bodies are also unusual but have been noted previously.[21]

The electron microscope findings serve to confirm that the material has the typical fibrillary structure of amyloid, but fixation was too poor to allow any conclusions to be drawn as to the relationship of the fibrils to component tissue cells, which is at present somewhat controversial.[12 13]

The reaction of the amyloid itself and associated giant cells to immunoperoxidase staining was too erratic for conclusions to be drawn.

The principal interest of the 2 cases is the apparent monoclonality of the cellular infiltrate associated with the amyloid. Thus, those cells that were labelled showed an overwhelming preponderance reacting for λ chains and IgA in case 1 and for κ chains in IgG in case 2. A greater proportion of the infiltrate reacted in case 2, probably because of the higher proportion of plasma cells. No previous immunoperoxidase studies appear to have been made on comparable cases, but in a case of orbital amyloidosis a suspension of cells obtained was stained with fluorescein-labelled antisera and found to show 30% of the cells reacting for IgG, 24% for κ chains and 4% for λ chains.[21] Since

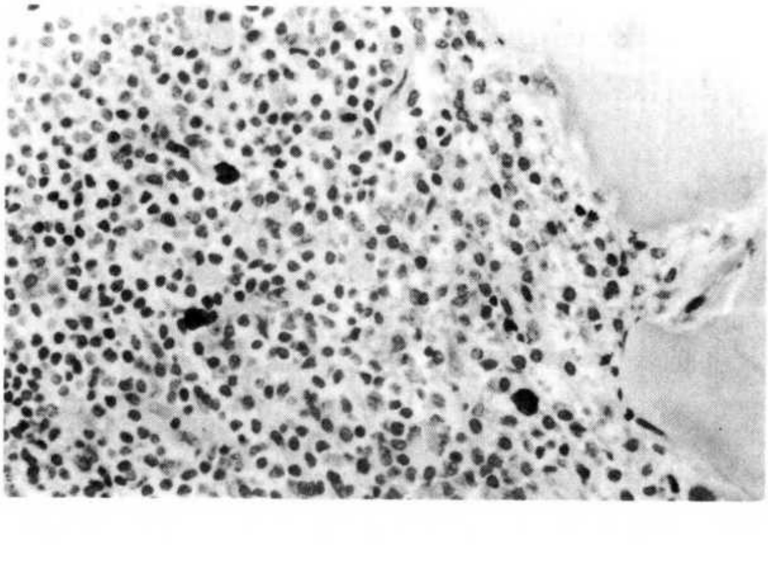

Fig. 9 Case 2. *Immunoperoxidase staining for λ light chains; only 3 stained cells in field comparable to that shown in Fig. 7. (×357).*

in normal serum 65% of the immunoglobulin molecules are of the κ type and 35% λ,[22] it is surprising that this was not considered by the author to indicate monoclonality.

The general pathogenesis of amyloid deposition has recently been comprehensively reviewed,[23-25] as also has its deposition in relation to the eye and adnexa.[2 26] The relative importance of immunocytes and macrophages remains controversial. Making the assumption that the lymphocytes and plasma cells associated with the amyloid infiltrates have a primary pathogenetic role, the apparent monoclonality of the populations is consistent with the view expressed by Glenner[25] that they represent 'burnt out' local extramedullary plasmacytomas. That there is no clear-cut boundary between orbital amyloidosis and pseudotumours[3] does not rule out such a conclusion because plasmacytic pseudotumours are difficult to distinguish from true extramedullary plasmacytomas except on the basis of the monoclonality or otherwise of their constituent cells.[27]

In view of the large local population of lymphocytes and plasma cells in the tarsal conjunctiva it is not surprising that the conjunctiva and lids are involved more frequently than the orbit. It is noteworthy that in case 1, in which the process apparently started in the orbit, the predominant heavy chain carried by the infiltrating cells was IgA, which is consistent with derivation of the progenitor cell or cells from the conjunctiva.

Note added in proof: Case 2 has developed a localised thickening of the eyelid at the same site after an interval of 2 years and 4 months. Tissue excised for cosmetic reasons and examined histologically contained amyloid with very few infiltrating cells.

Thanks are due to Mr I. M. Strachan, Mr S. K. Sharma, and Dr W. C. Walker for providing clinical details and to Miss K. Hughes and Mrs L. Thomas for skilled technical assistance. Professor W. L. Ford kindly read the manuscript and made helpful comments.

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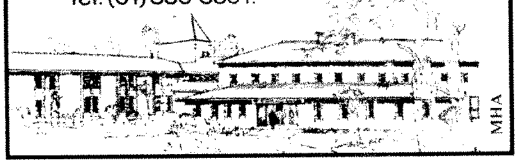

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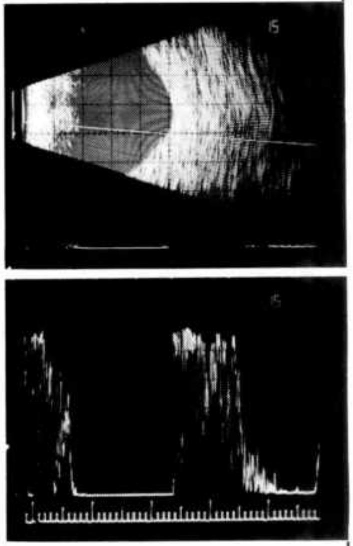

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British Journal of Ophthalmology, 1982, **66**, 607–609

Senile cataracts and the HLA system

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SUMMARY HLA A, B, and C typing was performed on a group of 309 southern Spanish people, namely, 207 controls and 102 patients who underwent a senile cataract extraction. Comparison of the results in the 2 groups (chi-square test) showed in the senile cataract group a significant increase in the association with HLA A9 ($p<0{\cdot}01$), HLA A blank ($p<0{\cdot}005$), HLA B5 ($p<0{\cdot}005$), HLA B13 ($p<0{\cdot}03$), and HLA B blank ($p<0{\cdot}01$) and a significant decrease in the association with HLA A2 ($p<0{\cdot}05$), HLA Aw24 ($p<0{\cdot}001$), HLA B27 ($p<0{\cdot}025$), HLA Cw2 ($p<0{\cdot}001$), and HLA Cw5 ($p<0{\cdot}01$). The factors underlying these increased and decreased associations are conjectural.

The major histocompatibility system of man (the HLA system) consists of many closely linked genes on the short arm of chromosome 6. Several loci can be distinguished. Some of them are responsible for graft rejection and are serologically defined (loci A, B, C, and DR), and another controls the mixed lymphocyte reaction (locus D).[1]

The association between the HLA system and several diseases has been reported by different authors.[2] In ophthalmology it has been reported in the cases of glaucoma,[3] anterior uveitis,[4] Behçet's disease,[5 6] retinitis pigmentosa,[7] and myasthenia gravis.[8]

Senile cataracts and the HLA system have been studied recently[9] without significant differences being found apart from a slight increase in the frequency of association with HLA A blank in relation to a control group.

Material and methods

A group of 309 southern Spanish people, 207 controls and 102 patients with senile cataracts, were studied. For an appropriate selection of the control group all those people suspected of suffering from a disease supposed to be related to the HLA system were rejected. The results were compared with those of other series in order to ascertain their significance value, the comparison being by the genetic identity index. The criteria for selection of patients with senile cataracts were: age 45 or over, family history negative, and the recorded character of the primary cataract.

HLA typing was performed by the Sección de Inmunología, Servicio de Análisis Clínicos de la Ciudad Sanitaria 'Virgen de las Nieves' de Granada, Spain, by the standard lymphocyte microcytotoxic test.

Results

The results are shown in Table 1. The chi-square test was used for a statistical analysis of the results. Values of p were calculated from the distribution of the chi-square[10] and by Fisher's exact test[11] (antigen B13). The significance level was predefined at $p=0{\cdot}05$.

Comparison between the 2 groups showed a significant increase in the association with HLA A9 ($p<0{\cdot}01$; $\chi^2=7{\cdot}425$), HLA A blank ($p<0{\cdot}005$; $\chi^2=8{\cdot}971$), HLA B5 ($p<0{\cdot}005$; $\chi^2=10{\cdot}210$), HLA B13 ($p<0{\cdot}03$; $\chi^2=4{\cdot}794$), and HLA B blank ($p<0{\cdot}01$; $\chi^2=7{\cdot}825$) and a significant decrease in the association with HLA A2 ($p<0{\cdot}05$; $\chi^2=4{\cdot}071$), HLA Aw24 ($p<0{\cdot}001$; $\chi^2=16{\cdot}302$), HLA B27 ($p<0{\cdot}025$; $\chi^2=5{\cdot}620$), HLA Cw2 ($p<0{\cdot}001$; $\chi^2=17{\cdot}962$), and HLA Cw5 ($p<0{\cdot}01$; $\chi^2=7{\cdot}587$). The relative risks appear in Table 1.

Discussion

The clinical interest of the HLA-associated diseases in ophthalmology has been reduced to the above-

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Table 1 *Phenotypic frequencies (PF) of the HLA antigens of loci A, B, and C in senile cataracts patients*

HLA antigen	*PF (%)*		*Relative risk*	χ^2	*p*
	Controls	*Patients*			
	(n=207)	*(n=102)*			
A1	23·18	22·54	0·96	0·016	
A2	46·37	34·31	0·60	4·071	<0·05
A3	17·39	9·80	0·51	3·104	
A9	6·76	16·66	2·75	7·425	<0·01
A10	8·21	8·82	1·08	0·033	
A11	14·97	15·68	1·05	0·027	
Aw19	1·44	1·96	1·36	0·112	
Aw23	0·48	0·00	0·0	—	
Aw24	18·35	1·96	0·08	16·302	<0·001
A25	5·31	4·90	1·07	0·024	
A26	0·96	2·94	3·12	1·674	
A28	3·86	2·94	0·75	0·170	
A29	14·97	17·64	1·21	0·365	
Aw30	8·69	14·70	1·81	2·588	
Aw31	1·93	1·96	1·01	0·0002	
Aw33	4·34	5·88	1·37	0·348	
A blank	21·25	37·25	2·19	8·971	<0·005
B5	10·62	24·50	2·73	10·210	<0·005
B7	15·94	13·72	0·83	0·260	
B8	10·14	14·70	1·92	1·381	
B12	2·89	3·92	1·37	0·228	
B13	1·44	5·88	4·27	4·749	<0·03
B14	15·45	9·80	0·59	1·861	
B15	8·69	7·84	0·89	0·064	
Bw16	3·38	7·84	2·43	2·945	
B17	4·83	1·96	0·39	1·508	
B18	15·45	13·72	0·87	0·162	
Bw21	8·69	6·86	0·77	0·309	
Bw22	5·31	2·94	0·54	0·889	
B27	9·17	1·96	0·19	5·620	<0·025
Bw35	20·77	17·64	0·81	0·421	
B37	0·48	0·00	0·0	—	
Bw38	0·48	0·00	0·0	—	
B40	8·21	6·86	0·82	0·174	
Bw42	0·00	0·98	0·0	—	
Bw44	17·05	20·58	0·69	1·526	
Bw45	1·44	1·96	1·36	0·112	
Bw47	0·97	0·00	0·0	—	
Bw48	0·48	0·00	0·0	—	
Bw49	0·48	0·98	2·05	0·263	
Bw50	5·31	4·90	0·91	0·024	
Bw51	6·76	0·00	0·0	—	
Bw52	0·96	0·00	0·0	—	
Bw62	0·00	0·98	0·0	—	
B blank	13·52	26·47	2·30	7·825	<0·01
Cw2	31·88	9·80	0·23	17·962	<0·001
Cw3	10·44	13·72	1·36	0·872	
Cw4	21·25	18·62	0·84	2·291	
Cw5	9·17	0·98	0·09	7·587	<0·01

mentioned conditions.[3–8] But the disorders of the lens and, above all, senile cataracts have been reported without conclusive results only once.[9] In that study an investigation of the HLA system in 60 patients suffering from senile cataract did not prove that they were associated and showed only an increase in the relation with HLA A blank against a control group. This may imply that HLA A homozygotes are more susceptible to this disease.

It was therefore thought we could work in an almost unexplored field because of the high frequency of disturbances in the transparency of the lens and the difficulty of their treatment and prophylaxis (apart from symptomatic cataracts).

Although nuclear sclerosis of the lens is a physiological process, not everybody develops an actual opacity; neither nuclear senile cataracts nor cortical opacities are universal. It follows that there is a difference between people suffering from senile cataract and the rest of the population. Without underrating the role of the phenotypic factors, environmental or not, we cannot exclude the possibility of a genetic factor, at least causing a predisposition. That is why the comparative study of HLA antigens in healthy people and in patients with senile cataract from the same geographic area was performed.

Our results may suggest that the antigens whose frequencies are significantly increased (in patients with senile cataract) point to a predisposing factor, whereas the antigens whose frequencies are significantly decreased point to a resistance or protective factor.

It can be assumed that the relationship between HLA and senile cataract is not very strong, and we cannot rely too much on an apparent association with different antigens. Nevertheless, as happens in other HLA-related diseases, the presence or absence of a specific antigen serves only as a predisposing or protective factor, but never involves a determinant character. Ankylosing spondylitis is a clear example of how only a low percentage of people who are HLA B27 positive suffer from the disease, though more than 90% of the patients possess the HLA B27 antigen.

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British Journal of Ophthalmology, 1982, **66**, 610–613

Uniocular Pulfrich phenomenon: an abnormality of visual perception

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SUMMARY We describe a patient with multiple sclerosis who experienced the Pulfrich illusion of elliptical motion of a target moving linearly when viewing the motion with *one* eye as opposed to the well recognised binocular manifestation of the phenomenon. The perception of the illusion was independent of the wave form or velocity characteristics of target motion or of retinal image position. We suggest that the occurrence of the phenomenon does not simply reflect delay in the visual system but is a function of an abnormality of perceptual interpretation of visual stimuli occurring at a high integrative level.

In 1922 C. von Pulfrich demonstrated that if a filter is held in front of one eye in a normally sighted individual a pendulum bob swinging in the frontal plane is perceived as moving with an elliptical trajectory.[1] His explanation of the phenomenon that has come to bear his name was that there was a prolongation of latency of vision in the dimmed eye. His theory was supported by the work of Julesz and White,[2] who extended the model of a 'delay-line' hypothesis to incorporate a short-term visual memory system with separate mechanisms for stereopsis and binocular combination, each having a different time constant. Frisen *et al.*[3] drew attention to the occurrence of the phenomenon in patients with minor optic nerve involvement from multiple sclerosis. We should like to report a case of an illusion with similar characteristics occurring with monocular vision and the results of some examinations.

Case report and investigations

A 29-year-old woman with definite multiple sclerosis and a positive family history of this disease presented initially 5 years ago with an episode of right retrobulbar neuritis. She had a further attack one year later. After recovery from the first episode she noted that, when she looked with the right eye alone, the trajectory of moving objects appeared distorted. When she viewed moving objects binocularly, the illusion was absent.

At the time of our examination there was temporal pallor of the right optic disc. Visual acuity on the right was 6/12 correcting to 6/4 with a pinhole, on the left 6/4. She saw 13 out of 14 of the Ishihara plates correctly but reported a subjective 50% desaturation to red with the right eye. Visual evoked responses in 1978 had shown a delayed latency on the right at 139 ms and a normal latency on the left at 98 ms. Half-field stimulation showed no additional disparity of latencies. The patient was a very accurate and reliable witness.

The behavioural characteristics of her monocular visual illusion were examined with a 5 mm diameter red target generated by a helium-neon laser reflected on to a screen at 2 m from the patient. The spot could be made to move in the horizontal or vertical plane with either a sinusoidal or ramp wave form subtending an angle which was variable up to a maximum of 44° of arc. The patient viewed the target both in darkness and with ambient illumination.

The target was made to oscillate at frequencies 0·002 to 10 Hz. The perceived trajectories at different frequencies are outlined in Fig. 1. The limiting frequency for the perception of motion which also produced autokinesis of the target was the same for each eye at 0·008 Hz. At 0·02 Hz the target, when viewed with the right (affected) eye, appeared to move in a half ellipse. Between 0·05 Hz and 5 Hz there was an illusion of elliptical motion. Above 5 Hz the right eye perceived linear motion, and at these higher frequencies the target had the appearance of a continuous line. When the target was moving from left to right it appeared to be approaching and

Correspondence to Dr J. J. Ell.

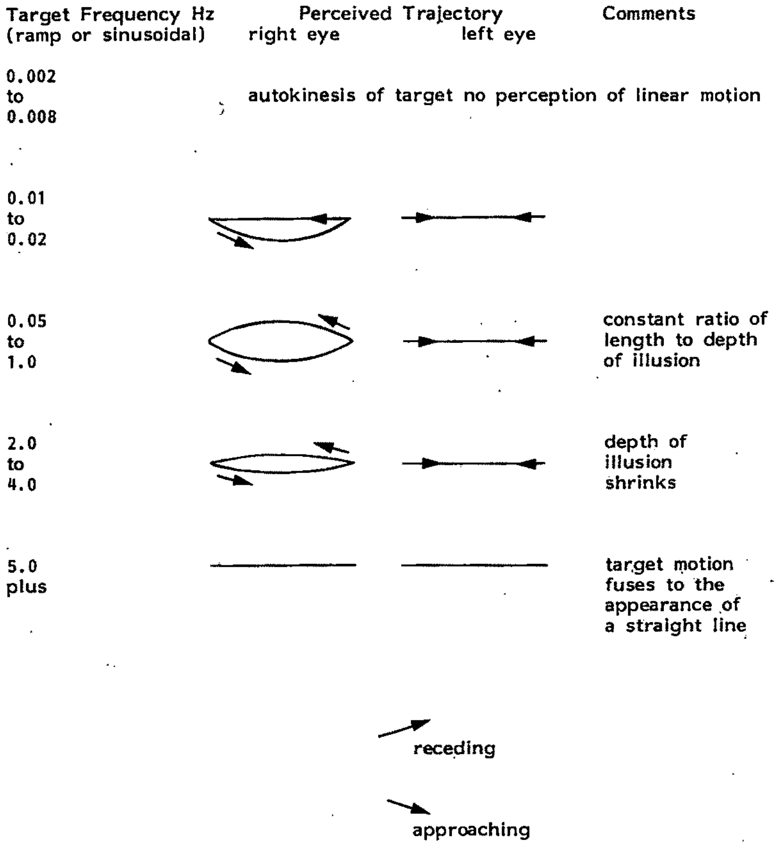
Target Frequency Hz (ramp or sinusoidal)
Perceived Trajectory
right eye
left eye
Comments
0.002 to 0.008
autokinesis of target no perception of linear motion
0.01 to 0.02
0.05 to 1.0
constant ratio of length to depth of illusion
2.0 to 4.0
depth of illusion shrinks
5.0 plus
target motion fuses to the appearance of a straight line
receding
approaching

Fig. 1 *Monocular manifestation of the Pulfrich illusion in the right eye of a patient with multiple sclerosis.*

enlarging; when moving right to left it appeared to recede and diminish in size. This directionality was found to alter from one test session to another. Targets moving unidirectionally always appeared to be approaching. Between 1 and 5 Hz the perceived 'width' of the ellipse diminished from 10 cm until a straight line was seen. The characteristics of the illusion were the same whether a sinusoidal or ramp wave form was presented and were identical both in darkness and with ambient illumination. The illusion occurred equally whether the patient attempted to track the target or maintained the eye in the primary position. The illusion as described was the same for target motion in the vertical plane. Objects truly receding and approaching were perceived normally. A target moving at 2 Hz with a saw-tooth wave form having a velocity asymmetry of 10:1 induced a very strong sense of ego motion in the direction of the fast phase. This was not experienced with the target moving at 1 Hz, nor was ego motion experienced at either frequency by normal observers.

Discussion

To our knowledge the occurrence of the Pulfrich phenomenon with monocular vision has not previously been reported. Its occurrence and characteristics as outlined raise important points concerning the explanation of the visual illusion. In the case of a normal subject with a filter before one eye the binocular disparity is proportional to the velocity of the target. In the case of a target moving in simple harmonic motion an elliptical trajectory is perceived. However, in our case presentation of a target moving at constant velocity did not alter the shape of the perceived ellipse. It is known that the perceptual latencies for foveal and extra-foveal stimuli are different.[4] Delay in visual perception[5] and in visual evoked responses (VER)[6] following retrobulbar neuritis has been clearly demonstrated. An alternative explanation of Pulfrich's phenomenon based on saccadic suppression has been put forward.[7] The fact that our patient noted no difference in the illusion while tracking the target as opposed to viewing it with the eye still is evidence against either the saccadic suppression theory or the explanation of differential delay between perception of stimuli perceived from the peripheral or central fields.

In his demonstration of the use of the Pulfrich pendulum as a method for detection of abnormal delay in the visual pathway of patients with suspected multiple sclerosis Rushton found a strong correlation between abnormality on the pendulum test and delay of the VER.[8] However, he was surprised to find no significant correlation between the size and direction of the interocular latency difference obtained from the Pulfrich pendulum and that obtained from the VER. As a possible explanation he suggested that small tracking variations may place the image on areas of retina of widely varying latency. This could be a possible explanation for the monocular Pulfrich phenomenon. Once again the fact that in our patient the illusion was not altered by foveal viewing as opposed to combined foveal and peripheral retinal stimulation is somewhat against this hypothesis. Rushton thought that cortical mediated mechanisms of depth perception were not implicated in the phenomenon, and our patient's observation that the presence or absence of ambient illumination made no difference supports his view in that she was not influenced by depth cues.

In view of the frequent occurrence of unilateral optic neuritis with corresponding delay in the VER one might ask why this phenomenon is comparatively rare. Furthermore the basic question arises: at what level in the visual system does the 'delay' take place? Observations to date would suggest that the Pulfrich phenomenon is due to an alteration in visual perception and thereby mediated primarily by the visual cortex. In their discussion Julesz and White postulated separate mechanisms for stereopsis (the localisation of binocular information in depth) and the cyclopean view (the binocular combination of the 2 eyes' views into a single percept). Each system could be thought of as having its own time constant for integration of successive images. For the case of the Pulfrich phenomenon on binocular vision they postulated a short-term visual memory with 2 different time constants. None of the current theories can explain the occurrence of the Pulfrich phenomenon with monocular vision. In our case the single requirement of the visual stimulus was that the subject could perceive target motion; depth cues, direction and velocity of motion, and retinotopic cortical localisation were unimportant.

Zeki[9] has established that the posterior bank of the superior temporal sulcus of the rhesus monkey contains neurones which signal motion of visual targets towards or away from the animal. These are termed opposed movement complex and hypercomplex cells. The source of cues to the directionality of target motion has to be binocular in the case of discrete point targets, for the signalling of direction relies on opposed directions of target motion movement on the 2 retinae. The directionality of a large target may be detected monocularly through displacement in opposed directions of the retinal images of various parts of the target. In the case of our patient a small target viewed monocularly was seen to approach or recede, although logically the perception of such motion in depth requires binocular input. These considerations afford a possible explanation of the monocular Pulfrich illusion, namely, that at a cortical level concerned with motion in depth there is a faulty processing of the visual signals which mimics the situation of a suitably opposed signal arising from the occluded eye. As such the phenomenon is analogous to synchiria.

It is evident that the illusion of motion in 3 dimensions experienced by our patient while viewing an object moving in a linear trajectory is not attributable to functional derangement of the retino-cortical projections and in particular is not a simple function of delayed conduction velocity. The reasons for this, reiterated, are that the shape of the trajectory of perceived motion was independent of the characteristics of the real motion of the target; in addition the illusion was not altered by foveal as opposed to combined peripheral and foveal viewing, the latter excluding an explanation involving different conduction velocities from different parts of the retina. That the illusion of elliptical motion in the case of our patient was dependent solely on the perception that something was moving and was otherwise unrelated to the physical parameters of motion suggests that the illusion reflects an abnormality of perceptual interpretation of visual stimuli occurring at a high integrative level.

We thank Dr P. Gautier-Smith for his kind permission to report this case.

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Book reviews

Molecular Processes in Vision. Eds. EDWIN W. ABRAHAMSON and SANFORD EUGENE OSTROY. Pp. 431. US$ 55·00. Academic Press: New York. 1981.

This volume is essentially a collection of published papers dealing with the biochemical basis of visual excitation, electrophysiology of the retina, and the relation of retinal events to responses in the visual cortex. There are also 5 articles written expressly for this collection. Each of the 6 sections has a brief editorial introduction setting the context for the papers which follow. Briefly, Part I deals with the biochemistry of rhodopsin, Part II with its photochemistry, and Part III with its disposition in the membrane of rod outer segments. Part IV covers the renewal process in photoreceptors and the role of the pigment epithelium, Part V biochemical studies of the transduction process, and the last part deals with electrophysiological observations from the photoreceptor level and leads up to a final paper on receptive fields in the striate cortex.

One may say at the outset that it seems an interesting notion to collect a series of important original contributions together in one place, although no doubt other editors would have made a different selection. We have a collection which will be useful for a scientist commencing work in this field who wishes to obtain a general idea of its progress during the last 20 years. That being granted, it must also be said that most of the papers reprinted should be available through any reasonable library and that in some instances, particularly where the original appeared in journals such as *Nature* or *Science*, the method of reproduction has led to some loss of quality in the text and in the half-tone plates. It is not easy to imagine what the readership for this book will be beyond that suggested above. Established workers in the field will already be aware of the contributions and will probably prefer up-to-date review volumes (and of course the current literature), and scientists outside the field may find the contents too specialised. This will inevitably restrict the appeal of the book. D. F. COLE

Exterior Lighting for Industry and Security. By STANLEY L. LYONS. Pp. 321. £20·00. Applied Science Publishers: London. 1980.

This work should be judged in terms of its purpose as a sort of recipe book for designers of exterior lighting, with especial reference to security. It is unfortunately sloppy and inaccurate, especially where it strays from that area. For example, in the opening section on vision the version of the well-known cross-section of the eye as shown in Fig. 1 has a lenticular cornea and a flat lens.

The author may have intended to rephrase scientific and technical definitions in down-to-earth English. Unfortunately his loose style renders the notorious photometric units more confusing than ever. It is stated on page 33 that the lumen is derived from the candela, whereas on page 34 the candela is 'accurately defined arbitrarily' in terms of the lumen.

These flaws must detract from the true worth of the book as a source of practical hints drawn from wide experience. There are details of various modern lamp types and their installation and maintenance as well as their applications in industrial areas. One has only to view a big urban area at night, especially from the air, to realise how important the subject has become, especially where there are security problems. The book meets a need for those who can pick through it critically. D. A. PALMER

Human Factors in Lighting. By P. R. BOYCE. Pp. 421. £26·00. Applied Science Publishers: London. 1981.

This unique and well-written book deals with all aspects of lighting in the most up-to-date way. Light, by definition, is visible electromagnetic radiation and necessarily involves humans, whence the title. Almost every conceivable interaction between lighting and people is touched upon. Dr Boyce has crammed many themes into a single, well-balanced volume.

The subjects include interior and exterior lighting designs of all kinds—industrial, commercial, recreational domestic, professional, and clinical. The logic of the ordering is peculiar, under whimsical chapter headings, but the arrangement of such a vast array of material is bound to be somewhat arbitrary. The assumption is of a reader at graduate level in a scientific or technical subject. Thus this is a good reference book for lighting engineers and scientists, not a student textbook. There are ample references for the specialist who seeks even more details. There are no obvious misprints or misstatements of fact.

D. A. PALMER

All About Glaucoma. By WOLFGANG LEYDHECKER and RONALD PITTS CRICK. Pp. 76. £4·95. Faber and Faber: London. 1981.

This little book is written for the hypochondriac patient, to answer all his doubts and apprehensions. Indeed the authors also might be labelled as rather overcautious: in reckoning that, where there is glaucoma in the family, even young children should be tested every 5 years; that, after operation, 'patients can usually leave hospital after about a week'; that, of over-40s, 2% have glaucoma, when the percentage with true glaucoma (significant field loss) is nearer a tenth of this.[1]

One could cavil too at odd linguistic assertions, like 'acute means sudden', 'acute=sudden' (actually acute means sharp-pointed), 'Glaukos means the Colour of the sea', and 'there is no special colour in a glaucomatous eye.' (Glaukos originally meant gleaming, then a light-grey colour, particularly of the eyes—as those of Athena—hence the 'glaucosis' applied by Hippocrates to blind eyes which looked murky, as they do in congestive glaucoma.)

It is rather chummy and personal in style ('we always recommend . . .'); and even if timolol is what they so often recommend, the authors do offer a fairly balanced picture, and the book will doubtless find a wide circulation in our increasingly health-conscious population.

P. D. TREVOR-ROPER

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Documenta Ophthalmologica Proceedings Series 28. Third International Conference on Myopia, Copenhagen 1980. Eds. H. C. Fledelius, P. H. Alsbirk, E. Goldschmidt. Pp. 253. Dfl.135·00. W. Junk: The Hague, 1981.

The transactions of the Third International Conference on Myopia are reported, and deal with several aspects of myopia. The subject grouping would indicate that research is chiefly concerned with the correlations of myopia, education, heredity, and scleral rigidity. Animal studies in monkeys elucidate the possible mechanisms of accommodation and internal eye pressure changes. There are also some contributions on pathological myopia and treatments to arrest myopia.

MONTAGUE RUBEN

The Visual Fields: A Textbook and Atlas of Clinical Perimetry. 5th edn. By DAVID O. HARRINGTON. Pp. 437. £27·00. Mosby: London. 1981.

The first edition of this book appeared in 1956 and its excellence as a practical guide to the examination of the visual field was quickly recognised. The main factors which have contributed to its success are a common-sense approach to the subject and plenty of good illustrations. The whole text is brought to life by the enthusiasm of the author for a method of examination which he believes to be of great clinical importance and with which the ophthalmologist himself must be closely associated.

Much of the revision undertaken since the fourth edition in 1976 is concerned with the introduction of new apparatus and techniques for examining the visual field, but the general arrangement of the book, with part I dealing with procedures and part II dealing with interpretation of results, has been retained. As examples of the changes we may note that descriptions of the Ferree-Rand perimeter, the Lloyd stereocampimeter, and Estermann's scoring grids for the tangent screen have been eliminated or curtailed, and in their place there appear accounts of the Baylor visual field programmer, the Fieldmaster, the Perimetron and the Octopus. Due acknowledgment is thus given to the contribution of new technology to the examination of the visual fields, but one sees clearly that the author believes that the ophthalmologist must not allow complicated automated apparatus to weaken his own involvement in the performance and interpretation of visual field tests. There is little need for much revision elsewhere in the book, though there is an increase in the number of substances which have to be mentioned in the section on toxic amblyopias, and CT scans have been added to illustrate cases in the sections on optic nerve, chiasma, and visual pathways.

Undoubtedly this edition maintains the high standard previously set.

J. GLOSTER

Intraocular Lenses. Ed. DALJIT SINGH. Pp. 225. £25·75. Praeger: New York. 1981.

Despite the fact that this book has been dedicated by the authors to 'the ophthalmologist who wants to learn more about intraocular lenses' it is really rather difficult to determine at which readers it has been directed. The book certainly gives an account of intraocular lenses and their usage up to 1979 and contains a lot of rather personal views in connection with the surgery. For an ophthalmologist already practising intraocular lens surgery it contains nothing new, and in fact the text is sadly out of date, as the subject has marched on a good deal since this book was assembled.

For the student seeking surgical guidance the text cannot be recommended, not so much because it is now behind the times but more because of some of the controversial material included. It is difficult to ignore statements to the effect that the superior rectus suture can be used to lift an eye out of a deep socket to facilitate surgery, but, more dangerously, the views expressed on indications and contraindications would be quite invalid in the UK.

A chapter is included on the insertion of intraocular lenses in very young patients, including infants, and I think that insufficient care has been taken to remind the reader that even in 1982 such views are not widely supported even in the United States.

This book deals in a way which is neither radical nor illuminating with a subject which has already been well covered in better texts, and I fear most purchasers would run the risk of being either disappointed or seriously misled.

A. D. MCG. STEELE

The Cranial Nerves. Eds. M. SAMII AND P. J. JANNETTA. Pp. 664. DM 180·00. Springer-Verlag: Berlin. 1981.

It is a great pity that the quality of this book is so patchy. It is an interesting attempt to synthesise anatomy, physiology, pathology, medicine, and surgery. Some of the reviews are very good (for example, Jannetta's chapter on the treatment of trigeminal neuralgia and hemifacial spasm), others are written in the most appalling English, which surely in a book written in English should have been corrected by the English-speaking editor, who should make sure that sentences like this do not appear: 'In newborns it is like a canal outlet to the intracranial side which in the mid-canal region and in the orbital exit looks like a rounded and on-point standing triangle or ellipse' (p. 77, referring to the optic canal). Unfortunately there are many other infelicities of style; arachnopathia pontocerebellaris may be perfectly meaningful to those of us who remember our Latin but not to others. For the ophthalmologist there are accounts of the anatomy of the optic nerve and chiasm, and there are chapters on the common compressive lesions of the optic nerves and chiasm. One chapter entitled 'Optic nerve compression by processes of the rhinobasis' is mostly about diseases of the paranasal sinuses. Ocular palsies due to aneurysms and pituitary adenomas are reviewed.

It is difficult to know at whom this volume is directed. It is hardly a comprehensive work of reference and most of its chapters are very difficult to read, and there is nothing which struck this reviewer as being of special interest to the ophthalmologist which could not be found elsewhere.

C. J. EARL

Current Ocular Therapy. By FREDERICK T. FRAUNFELDER and F. HAMPTON ROY. Pp. 647. £24·25. W. B. Saunders: Philadelphia. 1980.

Each author of this book has been asked to write a precis of today's treatment for a specific syndrome. On the basis of his experience he defines the syndrome, discusses systemic, supportive and ocular therapy, outlines ocular or periocular manifestations, describes precautions which are necessary in applying the recommended therapy, and ends by commenting on the disease and its treatment. The result is a most useful reference book and a thoroughly practical compendium. The personal aspect of the recommendations is helpful in that each author declares his preference when several options are offered in the way of therapy.

It is hardly a book which can be read through by the student or the trainee. It is rather a compendium of practical knowledge which should be handy for quick reference. For the practising physician in ophthalmology it is difficult to imagine a more helpful auxiliary, because each author has taken a special interest in the syndromes which he discusses, and they are chosen from all over the world.

STEPHEN MILLER

Molecular and Cellular Biology of the Eye Lens. Ed. HANS BLOEMENDAL. Pp. 469. £48·00. John Wiley: Chichester. 1981.

In a comprehensive account of the biochemistry of lens protein and the morphology of the lens particular attention has been paid to recent work on the cytoskeleton and contractile elements in the lens cell. This is further elaborated by a chapter devoted to the relationships between lenticular plasma membranes, the cytoskeleton, and microtubules. Detailed chapters on lens crystalline biosynthesis and the relationships between the crystalline of lower animals are also included. Proof of aging of lens proteins and the changes in their structure as seen in cataract are discussed. The final chapters deal with changes in concentration and enzymic activity due to aging and cataract formation. Particularly useful features of the book are the helpful concluding remarks and an extensive bibliography at the end of each chapter.

R. F. FISHER

Ocular Microsurgery. Developments in Ophthalmology. Vol. 1. Eds. A. S. M. LIM, L. C. Y. KHOO, and L. B. C. ANG. Pp. 95. Sfr. 50. Karger: Basle. 1981

This small volume contains a selection of articles and discussions presented at the World Convention on Microsurgery held in Singapore at the end of 1979. It proved to be important in promoting the extension of microsurgical knowledge and experience in the developing world. Ocular microsurgery is not covered systematically, but the topics indicate its wide scope. There is no index, and there are a few unfortunate misprints, but the book gives useful information to those wishing to make more effective use of the microscope.

M. J. ROPER-HALL

Notes

Cataract surgery

The New Orleans Academy of Ophthalmology will hold its 32nd annual symposium on cataract surgery on 16–20 February 1983. Details from Mr Bud Robinson, Executive Secretary, New Orleans Academy of Ophthalmology, Suite 512, 2025 Gravier Street, New Orleans, LA 70112, USA.

Glaucoma congress

A joint meeting of the 7th International Glaucoma Congress and 18th Annual Meeting of the American Society of Contemporary Ophthalmology will be held at the Sheraton Hotel in Bal Harbour, Florida, USA, on 13–19 March 1983. Details from John G. Bellows, MD, 211 East Chicago Avenue, Suite 1044, Chicago, Illinois 60611, USA.

Public health ophthalmology

A special master's degree programme in public health ophthalmology will be offered during 1983–4 by the Johns Hopkins Medical Institutions under the auspices of its International Center for Epidemiologic and Preventive Ophthalmology, a WHO collaborating centre. The programme is designed for persons interested in initiating, developing, and providing leadership to national or regional blindness prevention activities and in conducting serious clinical epidemiological research. Fifteen to 20 places are available for participants from developing and developed countries. Further information from Training Co-ordinator, ICEPO, Wilmer Institute, Johns Hopkins Hospital, 600 N. Wolfe Street, Baltimore, Maryland 21205, USA.

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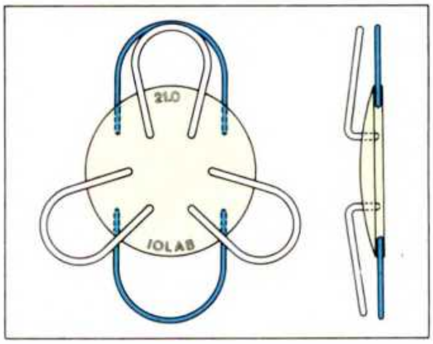

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Published by British Medical Association, Tavistock Square, London WC1H 9JR.
Typesetting by Bedford Typesetters Ltd., Bedford, England. Printed by Paramount Printing Co. Ltd., Hong Kong

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ASTM CODEN BJOPAL 66 (9) 549-616 (1982)

ISSN 0007-1161

British Medical Association Tavistock Square London WC1H 9JR

November 1982 Vol. 66 No. 11

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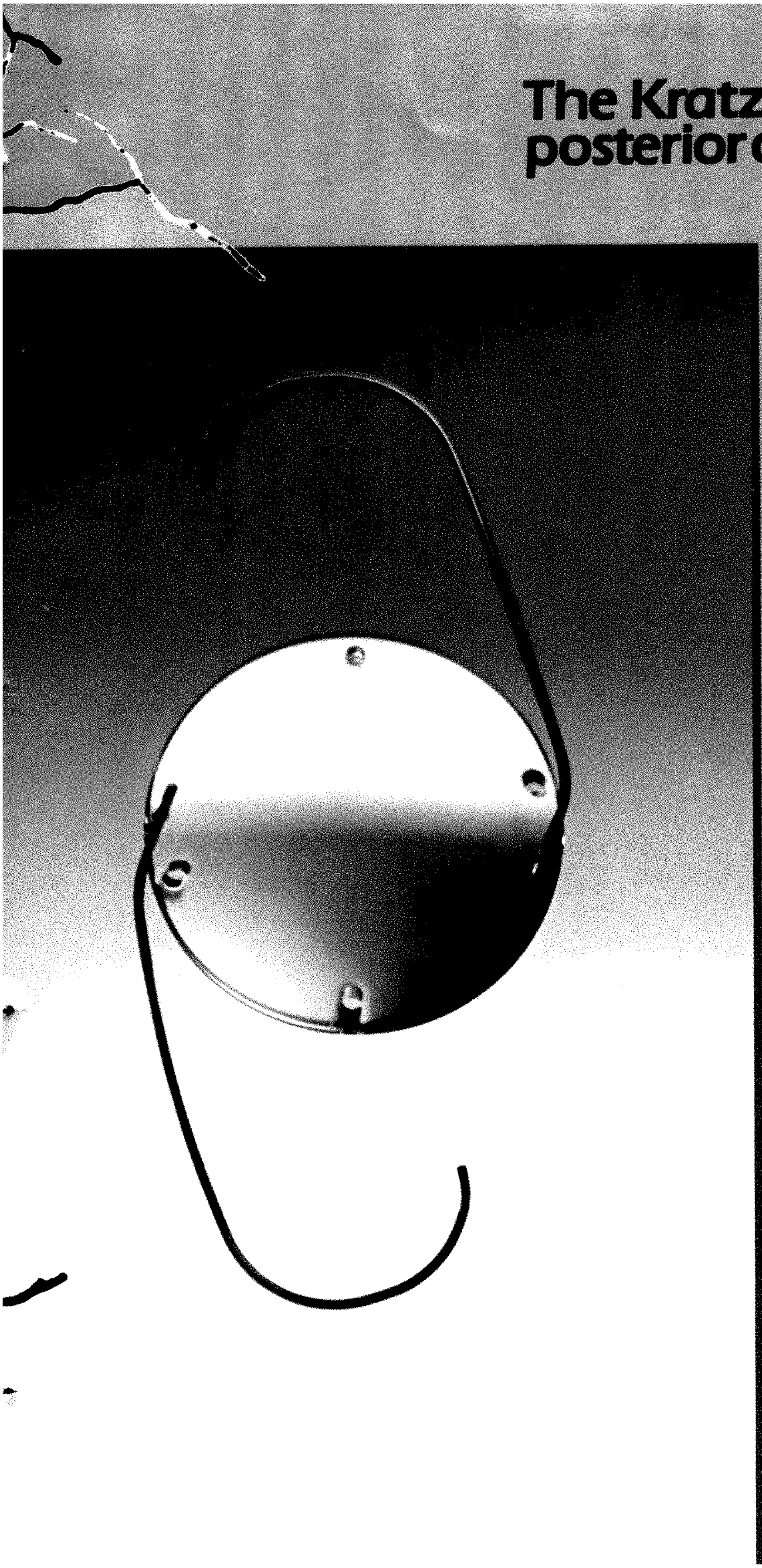

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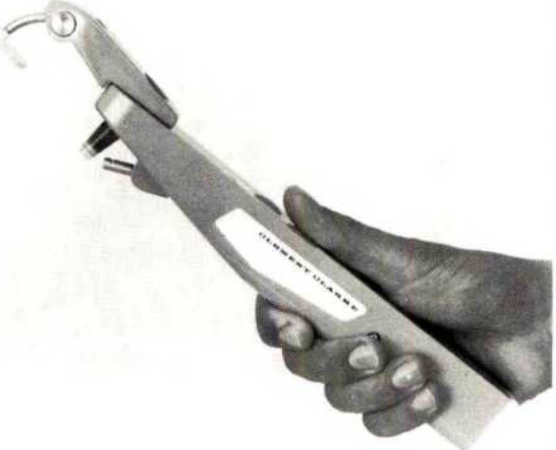

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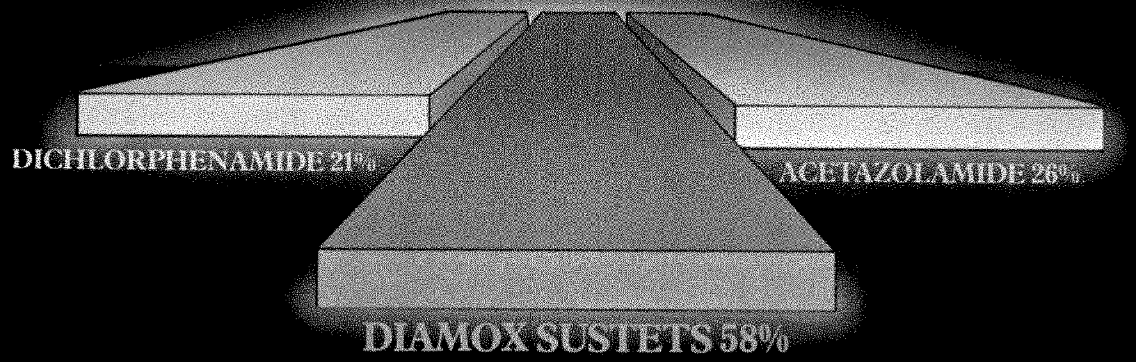

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British Journal of Ophthalmology, 1982, **66**, 685–690

Spontaneous regression of bilateral retinoblastoma

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SUMMARY A 24-year-old black man was found to have bilateral, spontaneously regressed retinoblastoma that had previously been misdiagnosed as post-traumatic chorioretinal scarring. His son and half-brother both had bilateral viable retinoblastoma. The ophthalmoscopic and fluorescein angiographic features of this patient's fundus lesions included a calcified, whitish mass located centrally in one of the scars and a fine residual vascularity in another of the fundus lesions. The authors review the pertinent literature on spontaneous regression of retinoblastoma.

Spontaneous regression is an uncommon but well-described feature of retinoblastoma,[1] which is estimated to occur in approximately 2 of every 100 tumours.[2] Clinical diagnosis of spontaneous regression can be made with relative certainty only in patients having viable retinoblastoma in the same or the opposite eye or in patients with a pathologically confirmed family history of retinoblastoma.

Unilateral, unifocal spontaneous regression of retinoblastoma is uncommon; bilateral multifocal spontaneous regression of retinoblastoma is even rarer. Yet several cases of this type have been reported.[3–13] In many of the previously reported cases the eye (or eyes) containing the spontaneously regressed tumour has been phthisical and blind.[6 7 12–17] Only a few reports describe preservation of the eyes and retention of useful vision in both eyes.[3–5 7 11] Even fewer of these cases have been well illustrated photographically.

This paper describes the case of a man with bilateral, spontaneously regressed retinoblastoma who retained useful vision in both eyes. The appearance of these lesions is illustrated with clinical photographs and fluorescein angiograms.

Case report

A 24-year-old black man (patient IIb in Fig. 1) was seen when his son was examined (patient IIIb in Fig. 1). He was found to have 3 lesions in the left fundus and one lesion in the right fundus. The son (patient IIIb) had just been found to have bilateral viable retinoblastoma. Inquiries into the family history revealed that the patient's half-brother (patient IIa in Fig. 1) had also had bilateral retinoblastoma and had previously undergone enucleation of one eye and photocoagulation and cryotherapy of a peripheral lesion in the opposite eye. Histopathological examination of the enucleated eye demonstrated a well-differentiated retinoblastoma.

Patient IIb reported having had poor vision since childhood in his left eye. A previous ophthalmic examination performed elsewhere had revealed exotropia, for which the patient had undergone horizontal rectus muscle surgery 5 years before our first examination. A macular lesion had been noted in the patient's left eye prior to this surgery, but it was diagnosed as a post-traumatic chorioretinal scar resulting from unrecalled ocular trauma. The patient's family history was negative at that time.

Ocular examination on the Oncology Service at

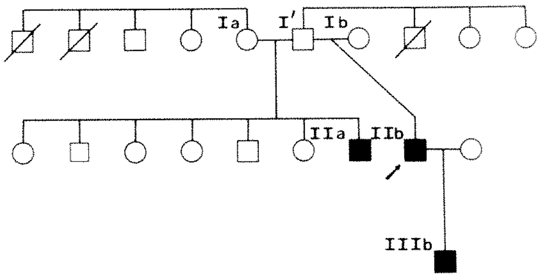

Fig. 1 *Retinoblastoma family pedigree.*

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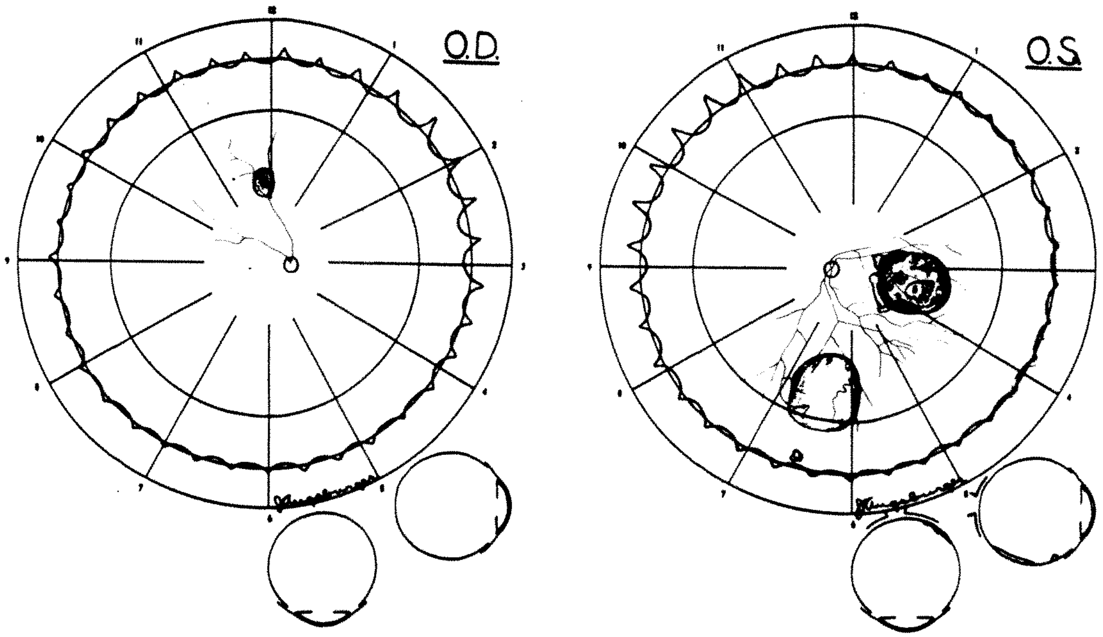

Fig. 2A Fig. 2B

Fig. 2 *Fundus drawings of right fundus* (A) *and left fundus* (B) *of patient IIb.*

Wills Eye Hospital revealed his best corrected visual acuities to be 6/5 in the right eye and 6/60 in the left. Intraocular pressures, measured by applanation tonometry, were normal. External examination disclosed conjunctival scars over the horizontal rectus muscles of the left eye. Slit-lamp biomicroscopy revealed no anterior segment abnormalities. Fundus examination of the right eye (Fig. 2A) showed a 3×2 mm minimally elevated grey-white lesion located about 9 mm superior to the fovea (Fig. 3A). The fluorescein angiogram of this lesion showed retinal pigment epithelial window defects (Fig. 3B). The overlying retinal circulation was intact, and there was no indication of a specific tumour circulation. The left fundus (Fig. 2B) contained 3 lesions. A 7·5×6 mm irregularly pigmented grey-to-black lesion was present in the macula (Fig. 4A). Near the centre of this lesion was an irregular, whitish, slightly elevated mass. There was an associated loss of the papillomacular nerve fibre layer. Fluorescein angiography demonstrated retinal pigment epithelial window defects without a retinal tumour vessel pattern (Fig. 4B). The second lesion in the left eye (Fig. 2B) was an 8×7 mm whitish-grey, gliotic-appearing, slightly elevated mass located about 5 disc diameters inferior to the fovea (Fig. 5A). The fluorescein angiogram of this lesion showed small, relatively discrete retinal pigment epithelial window defects as well as a finely branching pattern of small retinal tumour vessels (Fig. 5B). The third lesion was a very small, calcific nodule adjacent to the ora serrata at the 6:15-o'clock meridian (Fig. 2B).

A plasma carcinoembryonic antigen (CEA) test on patient IIb was slightly elevated at 3·7 ng/ml (normal range 0–2·5 ng/ml); the half-brother, patient IIa, had a plasma CEA of 6·8 ng/ml. (SI conversion: ng/ml= μg/l.) The parents of patients IIa and IIb were examined ophthalmoscopically and were found to have no fundus lesions. Patient I′, the father of both patients IIa and IIb, had a normal plasma CEA level.

Discussion

A number of well-documented cases of spontaneously regressed retinoblastoma have been reported in the literature. Many of the unilateral cases have been diagnosed on the basis of histopathological findings in patients with unilateral phthisis bulbi of unknown aetiology.[15] The characteristic histopathological features of spontaneously regressed retinoblastoma in such eyes include calcified tumour cell nests and necrosis of the surrounding retina.[15] Some patients with spontaneous tumour regression in a phthisical

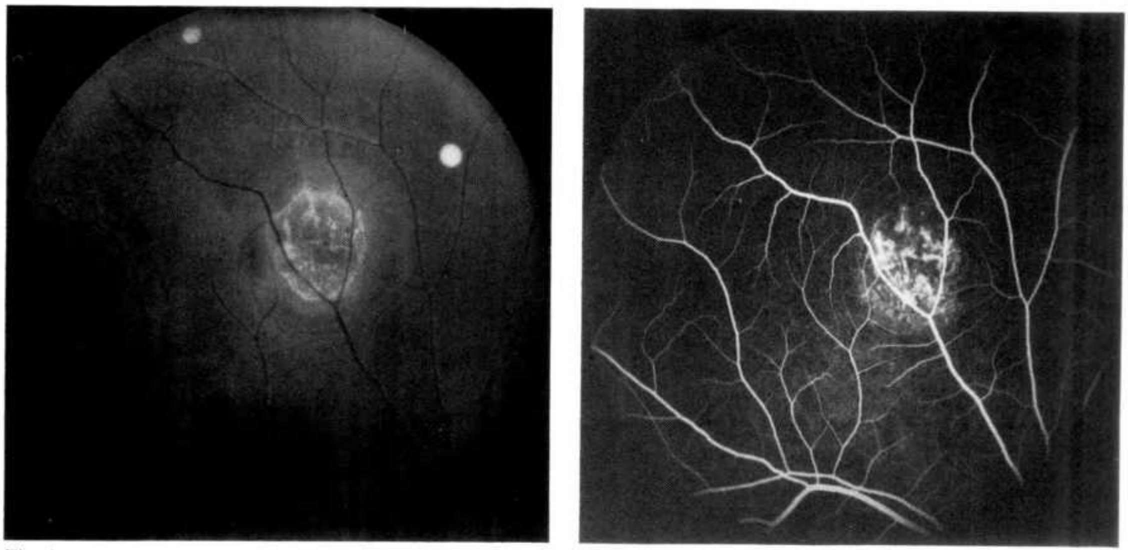

Fig. 3A Fig. 3B

Fig. 3 A. *Atrophic chorioretinal lesion in right fundus of patient IIb.* B. *Venous phase of fluorescein angiogram showing retinal pigment epithelial window defects.*

eye have been found to have viable retinoblastoma in the fellow eye.[6,14–17] A rare patient has even been found to have bilateral spontaneous tumour regression presenting as nontraumatic phthisis bulbi during childhood.[12]

Spontaneously regressed retinoblastomas in otherwise normal eyes have also been reported. Many such cases were diagnosed on the basis of a positive family history of retinoblastoma or the histopathological identification of retinoblastoma in the fellow

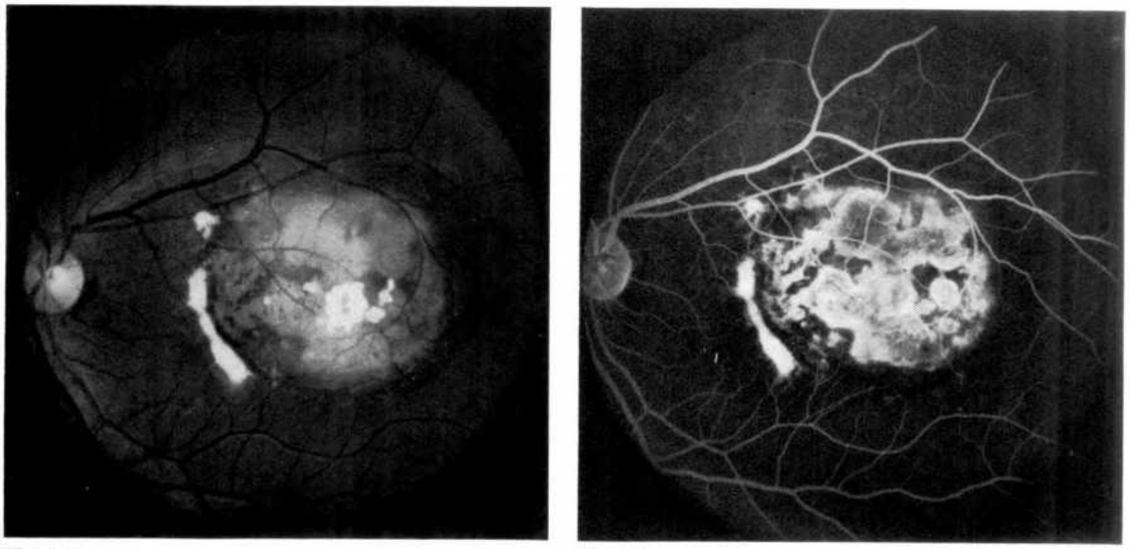

Fig. 4A Fig. 4B

Fig. 4 A. *Macular lesion in left eye of patient IIb. Note calcific retinal foci centrally within lesion.* B. *Recirculation phase fluorescein angiogram of macular lesion, which demonstrates retinal pigment epithelial window defects without tumour vessels.*

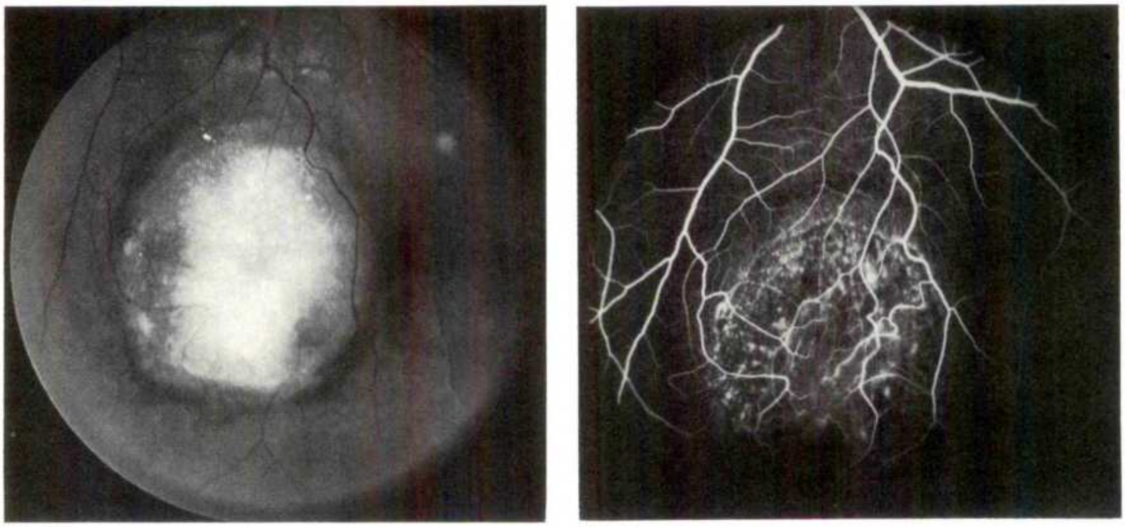

Fig. 5A

Fig. 5B

Fig. 5 A. *Inferior lesion in left eye of patient IIb.* B. *Venous phase fluorescein angiogram of lesion showing fine retinal tumour vessels.*

eye.[4–7 9–19] Other cases have been diagnosed by ophthalmoscopic observation of characteristic lesions in the fundi of patients with no family history of retinoblastoma.[20–23] The diagnosis of retinoblastoma must be considered presumptive in these cases.

The typical ophthalmoscopic appearance of spontaneously regressed tumours is generally described in terms of standard postirradiation regression patterns.[8] The macular lesion in our patient's left eye was consistent with a type I regression pattern with pronounced retinal-pigment epithelial alterations, and the inferior midperipheral lesion in this eye was similar to the type II regression pattern. The small, far peripheral inferior lesion in the left fundus appeared to be an entirely calcified type I lesion, but the small lesion in the right eye showed persistent fine tumour vessels. This observation is consistent with our findings in previously irradiated eyes with type I and type II tumour regression patterns.[24]

Regressed retinal tumours in otherwise normal eyes have been detected in both unilateral and bilateral cases of retinoblastoma.[3–5 7 9 11 19–23] Most of these eyes have retained useful vision, and many, containing one or more regressed tumours, have had normal visual acuity because the lesions were in extramacular locations. Our patient had normal vision in his right eye, which contained a single totally regressed extramacular tumour. However, his visual acuity was impaired in the left eye because of the macular location of one of the 3 regressed tumours.

There are several theories about the pathogenesis of spontaneous regression of retinoblastoma. One of the most popular is that regression occurs because of vascular insufficiency in a rapidly growing tumour.[1 25 26] According to this theory the tumour outgrows its blood supply, becomes necrotic, and subsequently regresses. Another theory suggests that an immunological mechanism may be responsible for spontaneous tumour regression. Histological deposits found in some retinoblastomas that have undergone spontaneous necrosis appear to be immune complexes,[27] and increased levels of circulating immune complexes have been found in some retinoblastoma patients.[28] Both our patient and his half-brother had

Table 1 *Comparison of spontaneously regressed retinoblastoma in a phthisical eye and spontaneously arrested retinoblastoma (retinoma)*

	Spontaneously regressed RB	*Spontaneously arrested RB*
Age at detection	Childhood to adulthood	Adulthood
Status of involved eye	Phthisis bulbi	Useful eye
Status of other eye	1. Viable RB 2. Retinoma 3. Normal 4. Phthisis bulbi	1. Viable RB (40%+) 2. Retinoma (25%+) 3. Normal 4. Phthisis bulbi
Mechanism of development	Obstruction of central retinal artery	Mutation of partially differentiated retinoblast

Table adapted from Gallie *et al.*[31]

elevated CEA, an antigen originally described in patients with gastrointestinal malignancies.[29] Some family relations of patients with retinoblastoma have been found to have elevated CEA, the 'CEA family syndrome.'[30] Whether there is any relationship between CEA levels and an immunological mechanism is unknown. There is no conclusive evidence that either the vascular or the immunological theory is correct.

We believe that the lesions in the patient described are regressed retinoblastomas, because they share ophthalmoscopic features and patterns known to occur in retinoblastomas following irradiation. However, 2 other suggestions can be made as to the nature of these fundus lesions. The first is that they are spontaneously arrested rather than spontaneously regressed retinoblastomas.[11] Smith considers that the histological and ophthalmoscopic appearance of these lesions is different from that found in regressed tumours after irradiation.[11] However, we do not know of any report of a growing, viable retinoblastoma which stopped growing spontaneously and assumed the appearance shown in his article.

The second suggestion is that proposed by Gallie and coworkers[31] (Table 1), who feel that this lesion is a nonprogressive retinoblastoma, a benign tumour which they have termed a retinoma. Their hypothesis is that a retinoma results when a genetic mutation occurs in a partially differentiated retinoblast. Had this mutation occurred in an immature cell, it would presumably have resulted in a viable, progressive retinoblastoma. No experimental or histopathological evidence has been presented, however, to show that this embryological sequence of events is correct.

Our patient had previously been misdiagnosed as having a post-traumatic chorioretinal scar, presumably as a result of a prior unrecalled ocular injury. The presence of calcified retinal foci within this macular chorioretinal scar, however, suggested the diagnosis of regressed retinoblastoma. We believe that ophthalmologists should be familiar with the characteristic appearance of regressed tumours and that they should consider retinoblastoma in the differential diagnosis of patients with typical fundus lesions. Correct identification of retinoblastoma at the time of our patient's examination for strabismus might have stimulated ophthalmoscopic examination of his son and half-brother at an earlier age. Then appropriate therapy[32] could have been initiated earlier and the chances of salvaging the eyes and preserving vision would have been better.

This work was supported in part by the Pennsylvania Lions Sight Conservation and Eye Research Foundation, Inc., the Retina Research and Development Foundation, the Ocular Oncology Fund, and the Research Department, Wills Eye Hospital, Philadelphia, Pennsylvania.

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British Journal of Ophthalmology, 1982, **66**, 691–694

Spontaneous regression of retinoblastoma in identical twins

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SUMMARY Spontaneous regression of retinoblastoma is described in identical twin boys. In the one bilaterally affected child 2 tumours regressed spontaneously, while a third lesion, which developed at a later stage, required treatment in the form of a cobalt plaque. The second child showed spontaneous regression of the single tumour in his only affected eye. The pathogenesis of spontaneous regression is discussed and a possible common aetiology in these 2 cases postulated.

Spontaneous regression of retinoblastoma is a term used by eye pathologists when calcified nests of tumour cells are found in an enucleated, often phthisical, eye, and by clinical ophthalmologists when fundal examination of a patient with retinoblastoma or relative has revealed, usually, an elevated calcified white mass, surrounded by areas of chorioretinal atrophy (no treatment ever having been given).

Retinoblastoma is unusual in the high incidence of spontaneous regression encountered (1·8%).[1–6] Several cases of bilateral retinoblastoma showed inert tumour in one eye with viable retinoblastoma in the fellow eye, while the spontaneous regression occurred in both eyes in only 12 of 47 cases reported.[7–9] Boniuk and Zimmerman[2] reported a pair of identical twins with unilateral retinoblastoma in whom the tumour spontaneously regressed in one child whereas an enucleation was required in the second child for a viable tumour.

This paper reports clinical spontaneous regression of retinoblastoma in a pair of identical twin boys in whom there was a positive family history of retinoblastoma.

Case reports

CASE 1

A Caucasian boy, one of a pair of identical twins born on 15 March 1973, was referred to an ophthalmologist at the age of 4 years 3 months after a health visitor had suspected reduced vision in the left eye. The children had been born 5 weeks prematurely, but milestones were normal. The only illness suffered was a bout of 'croup' at the age of 2½ years.

A positive family history of retinoblastoma was obtained, the father having had his right eye enucleated at the age of 3 years with the diagnosis proved histologically.

Examination under anaesthesia in July 1977 revealed spontaneous regression of tumours in both eyes. A small, inert tumour 3 mm in diameter was in

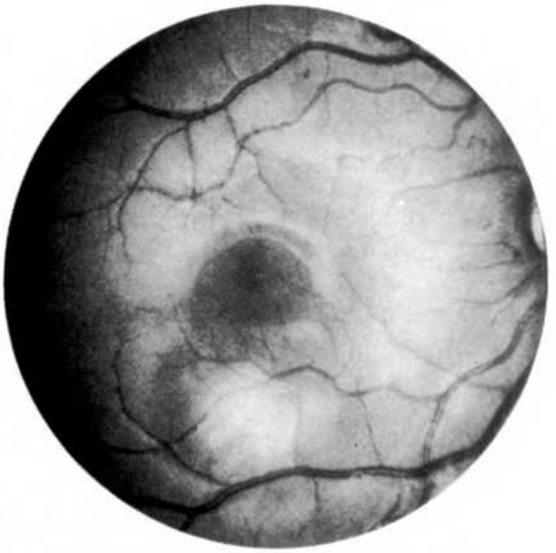

Fig. 1 *Case 1. Right eye. Inert retinoblastoma after spontaneous regression.*

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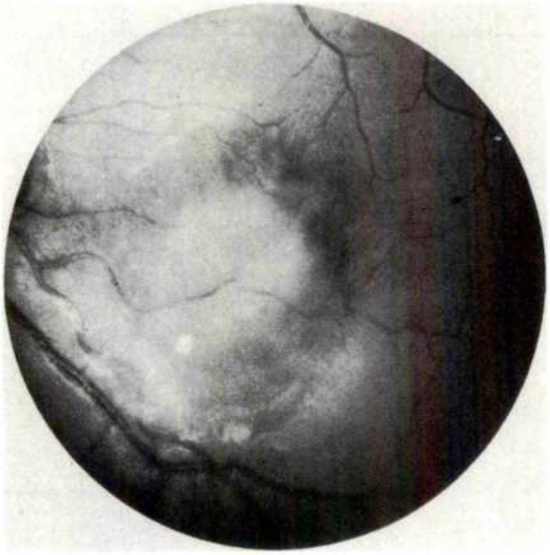

Fig. 2 *Case 1. Left eye. Paramacular lesion after spontaneous regression.*

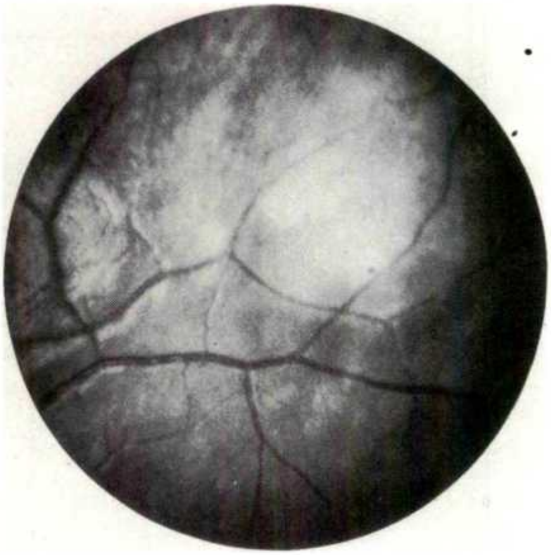

Fig. 4 *Case 2. Left eye. Spontaneously regressed retinoblastoma.*

the inferotemporal quadrant of the right eye below the macula (Fig. 1) while a paramacular lesion 5 mm in diameter (Fig. 2), with patches of calcification, was noted in the left eye. No evidence of past iritis was present.

On examination 6 weeks later a new, active tumour was noted in the upper nasal periphery of the right eye. This required focal radiation in the form of a D-shaped 10 mm cobalt plaque. The 2 original tumours remained unchanged.

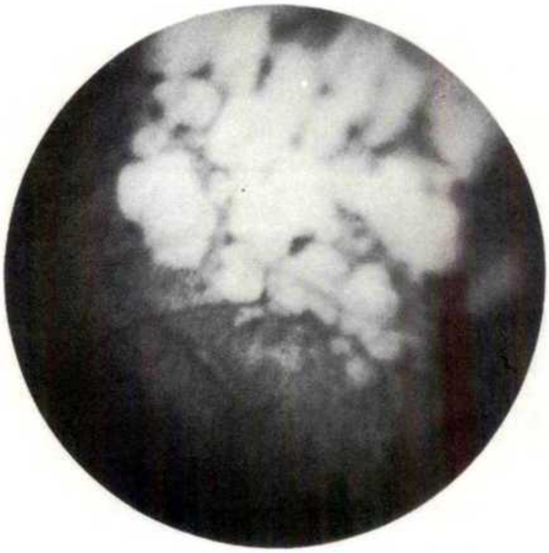

Fig. 3 *Case 1. Right eye. Inert retinoblastoma after cobalt plaque irradiation.*

Subsequent follow-up showed a good response to treatment. The lesion has remained inert until the present time (Fig. 3), as have the 2 other foci initially discovered.

The vision in the right eye is 6/9 unaided, and that in the left eye 6/36.

CASE 2

This boy was seen by an ophthalmologist after the diagnosis of bilateral retinoblastoma had been made in his identical twin brother (case 1). He had no visual symptoms and had no medical illnesses apart from mumps at the age of 3 years 9 months.

On examination under anaesthesia in July 1977 a spontaneously regressed tumour 5 mm in diameter was noted above the left macula. The right eye, however, was normal. At subsequent examinations the tumour has remained inert (Fig. 4) and has not required any treatment. No new lesions have developed.

CYTOGENETIC INVESTIGATIONS

The twins were typed for 16 different blood-group factors and they were identical in every respect. The frequency of polymorphic types and likeness of sex indicate a possibility for dizygotic twinning of only 0·02 (i.e., 98% chance that these twins are monozygotic). This probability is improved still further by the fact that their dermatoglyphic features were so very similar, both in pattern type and size, hand for hand. In summary, therefore, there is a 99% certainty of identical twinning. Their karyotypes were normal, without evidence of a 13q deletion.

IMMUNOLOGICAL STUDY

Lymphocyte transformation tests (March 1982). Allogeneic tumour cells obtained from enucleated eyes were suspended in 20 ml of 3 M KCl (pH 7.4) and left at 4°C for 24 hours with frequent shaking. The suspension was centrifuged at 40 000 *g* for 60 minutes and the supernate was dialysed for 16 hours against phosphate-buffered saline. The material was concentrated with lyphogel and sterilised by passing through a Millipore filter (0·22 μm).

The protein concentration was estimated by a modified Lowry method. Blood from the 2 cases was collected in preservative-free heparin (20 units per ml) and lymphocytes were separated by a density gradient technique using Ficoll-Hypaque preparation. Lymphocytes were cultured in medium 199 enriched with freshly prepared glutamine (2 mmol/ml) and the patients' own serum (1:10).

The test was carried out in quadruplicate in a microtitre plate in a gaseous phase of 5% carbon dioxide. Various concentrations of tumour extracts were added to the lymphocyte culture 24 hours after the initial incubation; 0·4 μCi of tritiated thymidine was added to each control and to experimental wells on the 6th day of the culture and incubated for a further period of 16 hours.

The lymphocytes were then harvested with a semi-automated harvester. The filter paper discs were transferred to scintillation vials and dried at 37°C for 3 hours; 10 ml of toluene-based scintillation fluid was added to each vial, and the radioactivity was measured in a Packard tricarb liquid-scintillation counter. The result was expressed as the lymphoproliferative—that is, transformation—index.

Case 1. The transformation index with allogeneic retinoblastoma was less than 2, which suggests that the patient was only weakly sensitised to tumour antigens.

Case 2. The transformation index with allogeneic retinoblastoma extract was 6, which suggests autosensitisation.

Discussion

The diagnosis of spontaneous regression of retinoblastoma in the above cases has been made on the basis of the characteristic clinical findings in the presence of a family history of retinoblastoma. The ophthalmoscopic appearance in spontaneous regression characteristically consists of one or more areas of chorioretinal atrophy in which elevated, irregular collections of chalk-white calcifications can be seen, often having the appearance of cottage cheese. Abnormal blood vessels are often found in the region of the tumour. This picture is similar to that following radiotherapy for retinoblastoma (Fig. 5).

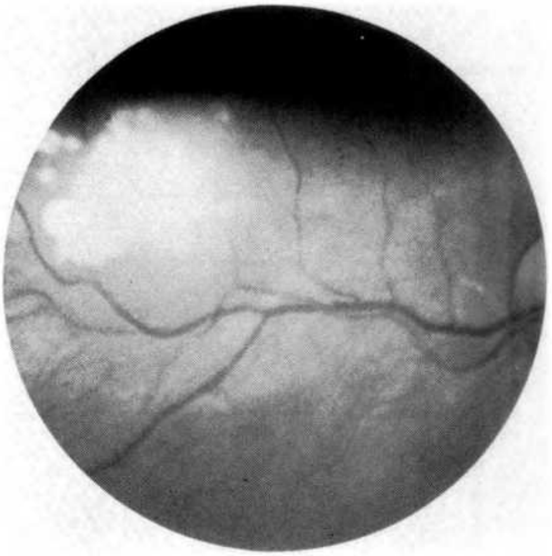

Fig. 5 *Regression pattern of retinoblastoma after external beam radiotherapy with the cobalt beam (3500 rads).*

The pathogenesis of spontaneous regression of retinoblastoma has not yet been fully established, but various hypotheses have been suggested to explain its occurrence, in particular tumour ischaemia and the host's immunological response. In the general sense growth of tumour cells is limited by vascular stasis and thrombosis resulting in capillary blockage in the neoplasm, relative to the proliferation and mass of the tumour itself. Areas of ischaemia may be accounted for by scanty stromal vascularisation, which in turn may be secondary to a lack of tumour angiogenesis factor or the inhibition of such a factor, either by some environmental factor or by an immune response.[10] Ischaemia alone, either accidental or from the tumour outgrowing its blood supply, is an unlikely explanation for the regression in these 2 cases of relatively small tumours.

It was suggested[11] that an acute febrile illness can trigger off a regression in the report of a case in which regression took place during scarlet fever at the age of 4 years. The fellow eye had been removed previously owing to retinoblastoma. Spontaneous regressions associated with acute febrile illnesses and other non-specific Freund's-adjuvant-type stimuli have been described in other malignancies, such as melanomas and carcinoma of the colon.[12] Both the 2 cases reported above suffered febrile illnesses some time before the tumours were initially discovered.

It must be presumed that the cell-mediated immune response to tumour antigens plays a significant part in the defence of the host against the tumour. In-vitro studies by Char and coworkers[13] showed high levels of cytotoxicity against labelled retinoblastoma cells in the evaluation of cell-mediated immunity to a retinoblastoma tissue culture line. In addition a cutaneous delayed hypersensitivity response was also elicited from the skin testing of patients with retinoblastoma with crude membrane extracts of retinoblastoma tissue culture cells.[14] A lowered host immune response may therefore be postulated in case 1 of this report and in other similar cases[3] in which some tumours regressed spontaneously, while others advanced. It is interesting that the results of the lymphocyte transformation test in case 1 suggested that the patient was only weakly sensitised to tumour antigens, in contrast to case 2.

Some local factor may be responsible in addition to the above. Calcium is an inhibitor of tumour growth, and it has been suggested that the excessive calcification often found in tumours showing spontaneous regression might lead to a toxic concentration of calcium and self-destruction of the tumour. However, it has never been proved that spontaneous regression is an effect of the calcification (which is also found in inert tumours treated by radiotherapy). The presence of the calcium deposits may, however, predispose the tumour cells to one of the other processes discussed above, which may in turn lead to spontaneous regression.

In conclusion, it is possible to postulate in the 2 cases reported above that some systemic factor, immunological or other and common to both children, allowed the spontaneous destruction of the tumours initially present. However, in one twin a subsequent tumour was not affected by this process and required treatment. Whether this would also have regressed spontaneously if the natural course of progression over a longer period was permitted is uncertain.

I am indebted to Michael Bedford, FRCS, for his permission to publish these cases, to Drs Rahi and Butler for their help with the immunological and cytogenetic investigations respectively, and to Sarah Dew for secretarial assistance.

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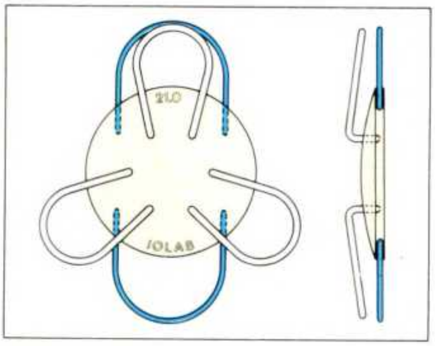

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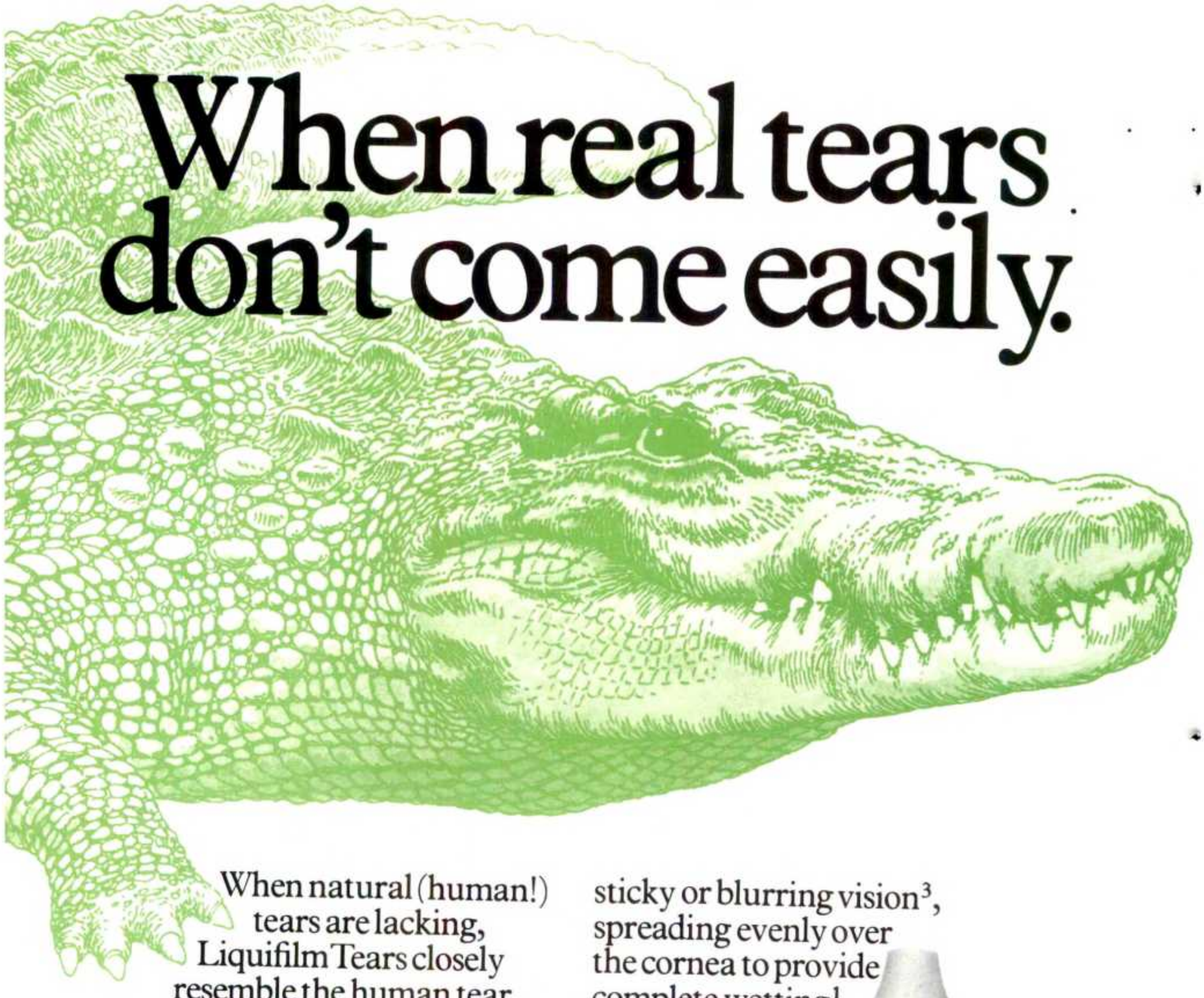

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British Journal of Ophthalmology, 1982, **66**, 695–704

Uveal melanomas presenting during pregnancy and the investigation of oestrogen receptors in melanomas

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SUMMARY We observed a young woman who showed growth of a choroidal melanoma over the course of 2 pregnancies, with subsequent enucleation of the eye. This is the first such documented case. In addition 4 other women with uveal malignant melanomas presented during pregnancy. This observed number of pregnancies (5) was greater than the expected number (2·1) among women of childbearing age who underwent enucleation with subsequent analysis in our pathology laboratory. However, this difference was not statistically significant. Further, more females 44 years of age or younger underwent enucleation for malignant melanoma than men of comparable age. Evaluation of these cases led us to propose that there is a subset of patients whose ocular melanomas are hormonally responsive. We therefore analysed uveal melanoma and choroidal tissue from 7 patients, including one of the pregnant women, for the presence of oestrogen receptors. No specific oestrogen binding was found. The possibilities that other hormones are involved or an immunological mechanism is operative are discussed.

Endocrine influences on cutaneous malignant melanoma have been explored for many years.[1–16] In contrast, the effect of endocrine factors on ocular melanomas has received little attention. A few anecdotal references[13 17 18] and case reports[19–22] of uveal melanomas occurring during pregnancy could be found in the literature. However, no one has reported whether or not growth of a uveal melanoma occurs during pregnancy or explored hormonal aspects of ocular melanoma or uveal tissue.

Studies of cutaneous melanoma on differences in incidence and mortality according to sex yield contradictory results.[1–6] The association between cutaneous melanoma and pregnancy or hormonal status among women is also equivocal.[1 7–16] Some report a better prognosis in women than in men[3] or in pregnant than in nonpregnant women.[4] However, a few find no significant differences in outcome according to sex,[4] pregnancy,[1 5–7] marriage status,[8 9] or use of oral contraceptives.[10]

On the other hand some epidemiological studies reveal a higher incidence and mortality for cutaneous melanoma in women of reproductive and menopausal age than in men.[11 12] Similarly, other reports suggest an unfavourable effect on prognosis when melanomas are exacerbated during pregnancy[13] or when stage II melanomas are related to pregnancy.[14] Activation of naevi or melanomas with use of birth control pills,[15] during pregnancy,[16] and after oestrogen administration[12] has been observed. Furthermore some animal studies imply changing growth patterns of skin melanoma in animals of differing hormonal status.[13 23 24]

Such clinical findings arouse the suspicion that some patients with cutaneous melanoma may respond to hormonal stimuli. Since uveal and skin melanocytes both derive from the neural crest, it is reasonable to propose that similar mechanisms may play a role in ocular melanoma.

Steroid hormone receptors have also been studied in an effort to understand hormonal influences on malignancies. The presence of steroid receptors in the cytoplasm of cells is characteristic of endocrine responsive tissue. Oestrogen binding activity has been

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found in 12 to 46% of cutaneous melanomas independent of the patient's sex or age.[25–28] Since steroid hormones may be involved in the pathophysiology of various human malignancies or may be useful as therapeutic regimens, as in breast cancer, looking for receptors in cancer tissue makes good biochemical sense.[29]

We herein report 5 cases of young women who presented with uveal malignant melanomas during pregnancy, one of whom is the only well documented case in the literature of growth of ocular melanoma associated with pregnancy. The possibility that there might be a subset of patients whose ocular melanomas are hormonally responsive was raised. Since oestrogens are the major trophic hormone of pregnancy, a biological response of uveal tissue to oestrogens was proposed. To test this hypothesis, we analysed uveal melanomas and adjacent uveal tissue after enucleation for the presence of oestrogen receptors, and, as will be discussed, none were found.

Subjects and methods

CASES

We recently observed 2 patients with ocular melanoma presenting during pregnancy. This led us to review our series of melanomas in the Pathology Laboratory at the Massachusetts Eye and Ear Infirmary (MEEI) from 1953 through 1973 and we identified specimens from 3 other pregnant women with ocular melanoma. Paraffin embedded, formalin fixed tissue was processed for light microscopy. Slides were stained with haematoxylin and eosin or periodic acid-Schiff, and potassium permanganate treated (bleached) sections, when indicated, were obtained. We examined the slides, verified the diagnosis, and described characteristics of the tumours in each case. A specimen from the tumour which grew during 2 pregnancies (case 1) was studied by electron microscopy by techniques previously described.[30 31]

Follow-up procedures on the 4 living patients involved personal contact with the patients as well as documentation of their status from their ophthalmologists and internists. Two patients died, and discharge summaries and slides of biopsies were examined to confirm the cause of death.

The age and sex distributions of patients who had an enucleation for uveal malignant melanoma with subsequent pathology analysis at the MEEI over the same time period as the 5 cases were evaluated. Female and male ratios for patients 44 years of age or younger were calculated. Birth rates for all women in the United States adjusted for age and year of birth[32] were then used to calculate the cumulative probability of being pregnant for each woman 44 years of age or younger. These probabilities were then added to obtain the expected number of pregnancies among women in this age group. The significance of the difference between the observed and expected number of pregnancies was then determined by the Poisson distribution.

OESTROGEN RECEPTOR ANALYSIS

Uveal melanoma tissue (at least 2 mm^3) was collected under sterile conditions from 5 cases as soon as possible after enucleation and frozen in liquid nitrogen. One of these specimens was from the eye of a pregnant young woman discussed in this report (case 1). At the same time normal choroid was collected from an area adjacent to the tumours to serve as control tissue. Delays of 4 and 7 hours in processing tissue were encountered in two other cases (one necropsy and one from a distant institution), and these cases were analysed as negative controls.

Oestrogen receptor assays were carried out on the tumour and choroidal tissue cytosols according to methods used for the analysis of oestrogen receptors in human breast cancers in the laboratory performing breast receptor assays for the Massachusetts General

Table 1 *Clinical and pathological data on 5 cases of uveal melanomas presenting during pregnancy*

Patient (accession number)	*Age race*	*Month of pregnancy*	*Presenting complaint*	*Melanoma*			*Outcome*
				Location	*Size*	*Cell type*	
1 (E80–923)	27 W	7 (1st) 6 (2nd)	Ocular pain OS for 2 days	Choroid	Medium	Mixed	Normal delivery dead due to metastatic melanoma
2 (E80–1275)	33 W	7	Blurred vision OD for 2 days	Choroid	Small	Spindle B	Normal delivery alive and well
3 (E56–341)	35 W	5	Blurred vision OD for 2 weeks	Choroid	Small	Spindle B	Normal delivery alive and well
4 (E69–746)	22 W	6	Blurred vision OS for 4 days	Choroid	Large	Spindle B	Normal delivery dead due to metastatic melanoma
5 (E61–497)	29 W	4	Injection OS, history of glaucoma and 'cyst' OS	Iris, ciliary body	Small	Spindle B	C-section alive and well

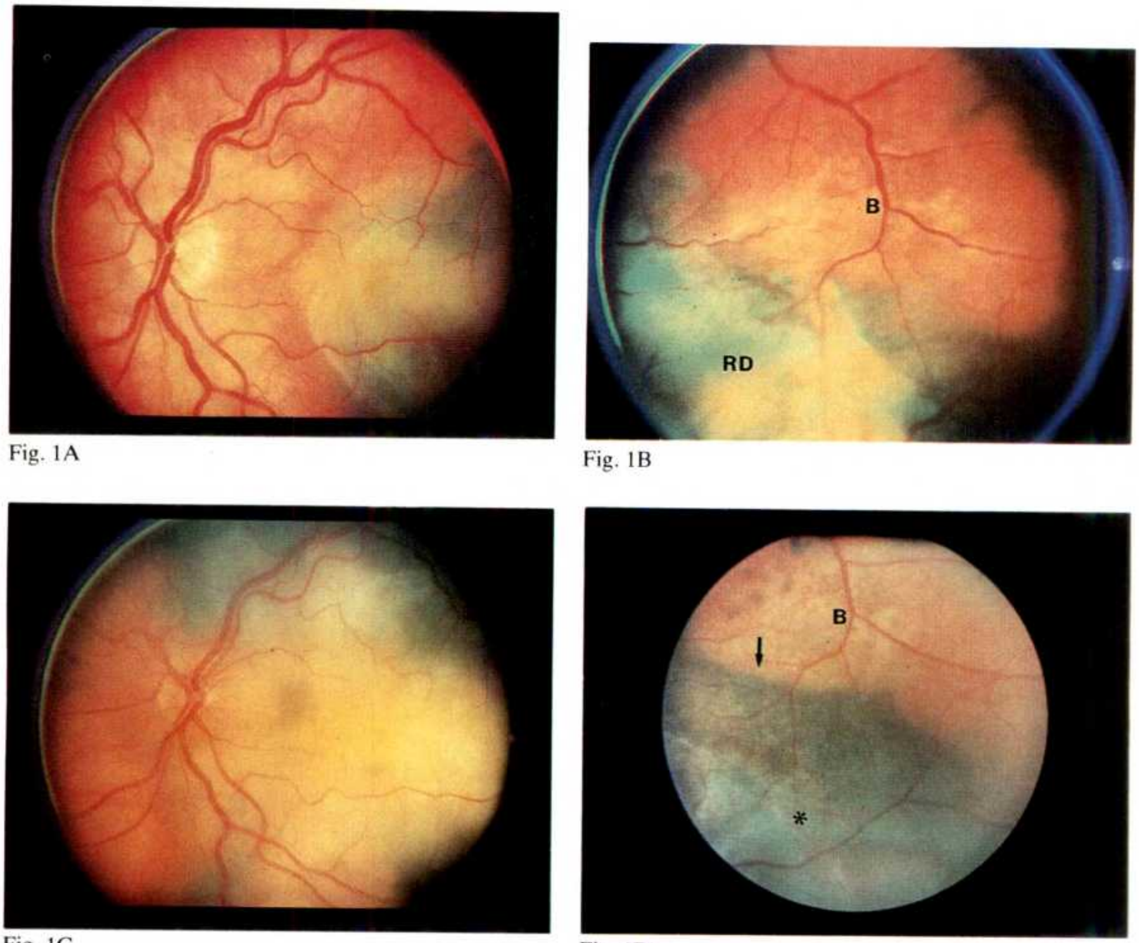

Fig. 1A

Fig. 1B

Fig. 1C

Fig. 1D

Fig 1 *Case 1.* (A) *Pigmented mass involving the macula OS during her first pregnancy, November 1978.* (B) *Edge of the lesion in November 1978, showing retinal detachment (RD). Bifurcation of vessel (B) used as a landmark for comparison in Fig. 1B and Fig. 1C.* (C) *Edge of the mass in between her 2 pregnancies showing a decrease in the subretinal fluid (*) with straightening of the vessels.* (D) *Tumour surrounding the optic disc as seen immediately following delivery of her second child in June 1980.*

Hospital (Vincent Research Laboratories and DTM).[33 34]

Since the tumour samples were small (tumour average net weight 98 mg, choroid average weight 61 mg), duplicate single saturating dose assays at 2 nM ^{3}H oestradiol in the absence and presence of 250-fold molar excess of unlabelled diethylstilbestrol were performed.

Results

Five white women ranging in age from 22 to 35 presented during their fourth to seventh months of pregnancy with uveal malignant melanoma (Table 1). All delivered full-term normal infants. Two of them subsequently died of metastatic malignant melanoma.

CASE 1

This 27-year-old white female was first seen on 30 October 1978, with the complaint of pain in the left eye of 2 days' duration followed by oedema and redness of the eyelids and decreased vision. At this time she was 7 months pregnant. There was no significant past ocular history. She had been on birth control pills from about March 1977 to March 1978. Family history revealed that her mother died of stomach cancer. Her last ocular examination, in April 1973 by an optometrist, revealed normal visual acuity in both eyes.

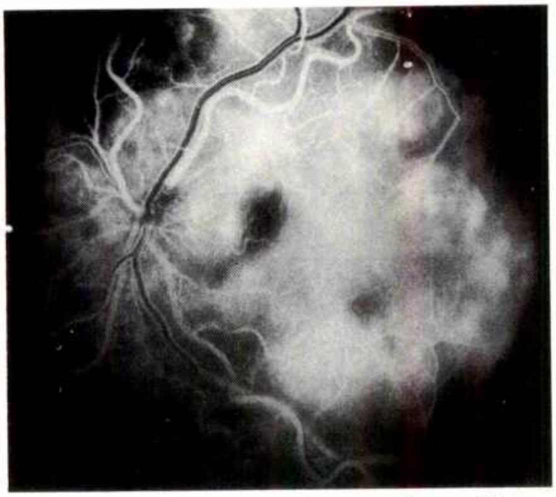

Fig. 2 *Case 1. Fluorescein angiogram of the mass OS during arteriovenous phase showing hyperfluorescent areas.*

Ocular examination of the right eye was normal. Visual acuity OS was counting fingers at 1 foot (30 cm). Visual field examination revealed a central scotoma, almost complete loss of the superonasal quadrant, with marked constriction superotemporally. She had moderate oedema and erythema of the lids, with minimal conjunctival injection and chemosis. There was an afferent pupillary defect. Ocular motility was normal. Slit-lamp examination of the cornea and anterior chamber was unremarkable. Applanation intraocular pressures were 15 mmHg, 10 mmHg OS. In the fundus of the left eye was a dark lesion measuring about 3×4 disc diameters located 1½ disc diameters temporal to the disc involving the macula (Fig. 1A). There was some pigment proliferation and mottling at the temporal border of the lesion. A large serous detachment extended from 2.30 to 8.00 o'clock. Ultrasonography revealed a lesion 2 mm in height with no choroidal excavation.

The differential diagnosis at this time was subretinal pigment epithelial haemorrhage or malignant melanoma. It was decided that because of her pregnancy, further testing would be delayed. The lesion remained stable during the latter part of her pregnancy.

She was then delivered of a normal daughter on 29 January 1979. She did not resume birth control pills and again became pregnant in August 1979. During this interval between pregnancies the subretinal fluid decreased (Figs. 1B,C).

Suddenly on 1 February 1980, 6 months into her second pregnancy, she had a recurrence of the ocular pain and irritation OS similar to her experience during her first pregnancy. Her visual acuity had not changed. There was minimal conjunctival injection and the globe was tender to palpation. There were a moderate number of cells in the anterior vitreous OS. The pigmented lesion in the left eye was slightly larger, extending superior and inferior to the disc with irregular margins. There was a bullous retinal detachment extending from 2.00 to 9.00. There did not appear to be an increase in height. Again, because of her pregnancy, further testing was not performed.

She was delivered of a normal son at term on 27 May 1980. In June her visual acuity was counting fingers at 5 feet (150 cm) OS. Fundus examination revealed that the pigmented tumour was even larger than before, and it surrounded the optic disc (Fig. 1D).

Fluorescein angiography was performed and revealed several hyperfluorescent areas in the early and middle phases of the angiogram which progressed during the transit and leaked, consistent with vascular areas seen in melanomas (Fig. 2). Ultrasonography revealed a solid lesion with some suggestion of acoustic shadowing in the orbit. Choroidal excavation was not definitely seen.

A clinical diagnosis of malignant melanoma was made. Because the lesion had grown and her visual acuity was poor, enucleation was advised. Liver function tests including bilirubin, alkaline phosphatase, and SGOT were normal. Enucleation of the left eye was performed on 28 July 1980.

She remained well until January 1982, when biopsy-proved liver metastases developed. Chemotherapy was initiated, but she died in April 1982 of widespread metastases.

Pathological examination. On gross examination of the eye a pigmented choroidal tumour was seen surrounding the optic nerve. It extended 10 mm temporally from the disc and 2 mm nasally. The temporal aspect of the tumour was a circumscribed mass elevated 3 mm, while the remainder of the tumour had a more flat, diffuse configuration with an elevation of 1–2 mm (Fig. 3A). The retina was totally detached.

Histologically the tumour contained areas of dense connective tissue (Fig. 3B). Spindle A, spindle B, and epithelioid cells were present, with a diagnosis of mixed cell type.[35] There were nests of naevus-like cells at the edge of the tumour adjacent to the optic nerve. Tumour cells were seen invading the optic nerve anterior to the lamina cribrosa and scleral emissary canals (Fig. 3C). Bruch's membrane was not ruptured. A moderate amount of chronic nongranulomatous inflammation was present within the tumour. The retina was detached, and areas of associated retinal pigment epithelium had undergone fibrous metaplasia. The cornea, anterior chamber, lens, iris, and ciliary body appeared normal. Electron microscopy of this melanoma revealed bundles of collagen

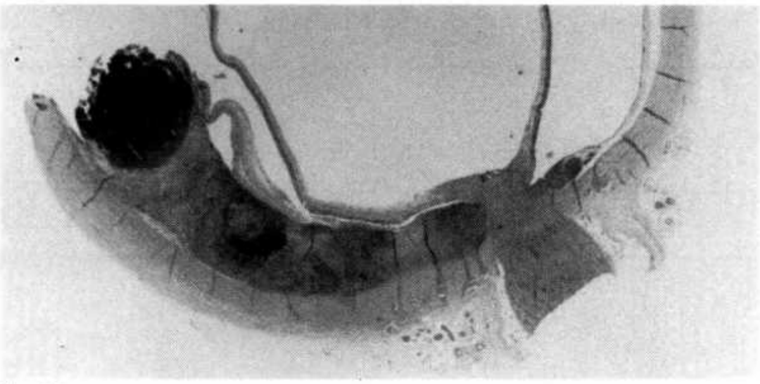

Fig. 3A

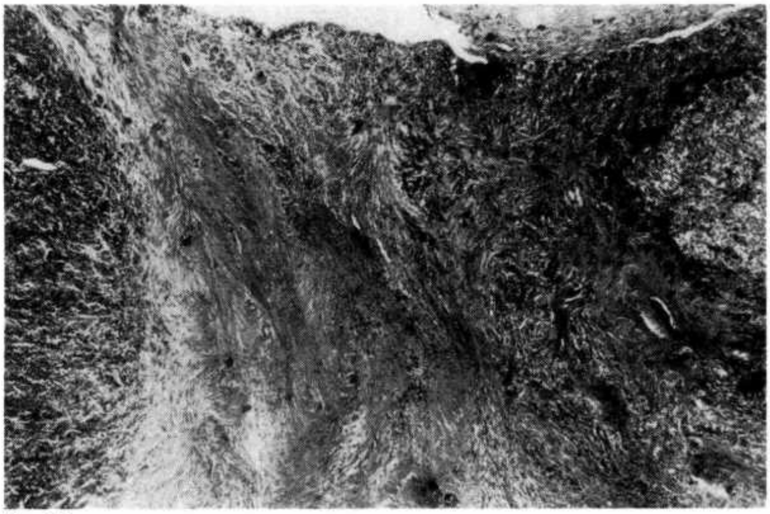

Fig. 3B

Fig. 3 *Case 1.* (A) *Choroidal tumour with diffuse configuration. (Haematoxylin and eosin, ×5·8).* (B) *Dense connective tissue within the tumour. (Haematoxylin and eosin, ×42).* (C) *Peripapillary tumour with invasion of the optic nerve (arrow). (Haematoxylin and eosin, ×26·5).*

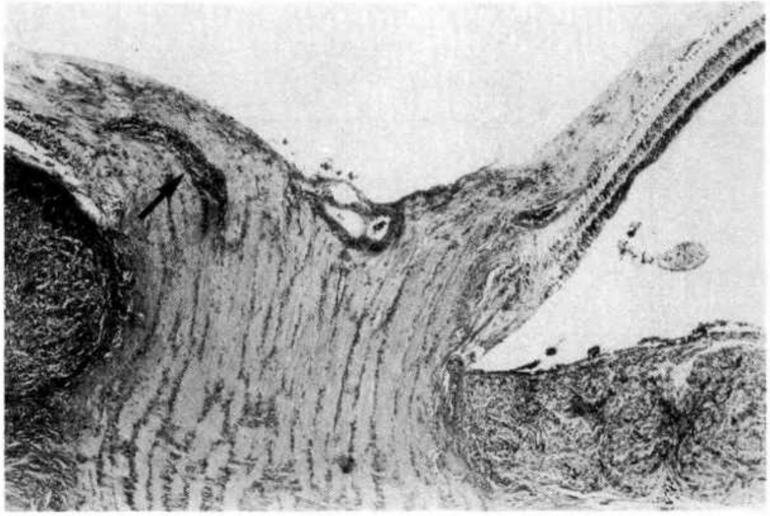

Fig. 3C

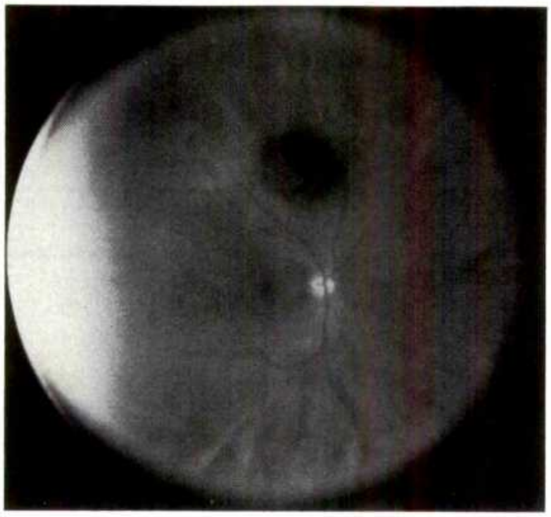

Fig. 4 *Case 2. Wide angle photograph of pigmented mass superior to the disc OD.*

fibrils amid tumour cells in areas of connective tissue seen on light microscopy.

CASE 2

This 33-year-old woman presented in her seventh month of pregnancy with a 2-day history of her vision being obstructed by a 'veil' OD. Her last reported visual acuity was 20/20 OU in November 1977, when she was treated for an allergic conjunctivitis. There was no other significant past ocular history.

Her visual acuity was 20/100 OD and 20/20 OS. External and anterior segment examination was entirely within normal limits OU. Applanation intraocular pressures were 18 mmHg OU. Fundus examination of the right eye revealed a pigmented lesion 5 mm in diameter, 2 mm elevated located 3 to 4 disc diameters superior to the disc OD (Fig. 4). A secondary serous detachment involving the macula was present. The fundus of the left eye was normal.

A number of consultants agreed that the lesion was a malignant melanoma. Various treatment possibilities including observation for evidence of growth, enucleation, and alternative methods, such as proton beam irradiation, were discussed. When the patient learned that she had a tumour in her eye she insisted on prompt enucleation and would not consider alternative therapies. Her alkaline phosphatase level was normal. Enucleation was then performed on 14 October 1980. The size of the tumour was too small to warrant sampling for oestrogen-receptor analysis.

The patient did well subsequent to her enucleation and was delivered of a normal son on 12 December 1980. Thus far she and her son have remained in good health with no systemic medical problems.

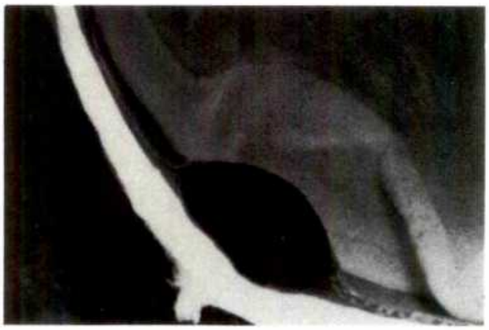

Fig. 5A

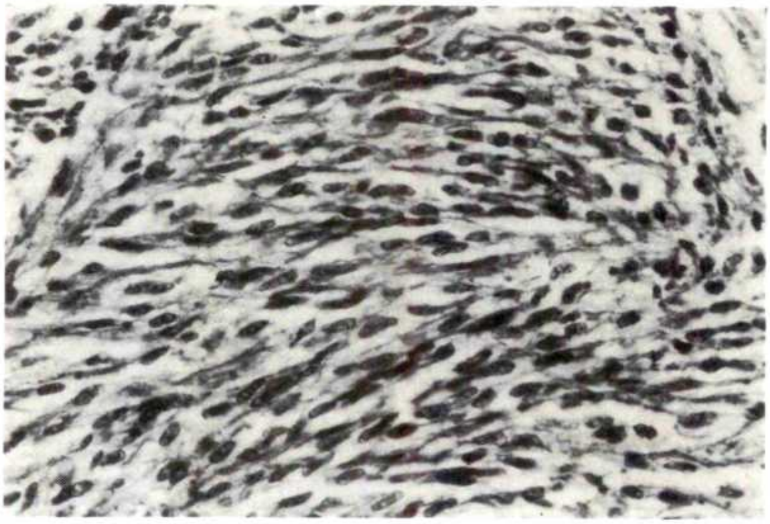

Fig. 5B

Fig. 5 *Case 2.* (A) *Tumour arising from the choroid in the posterior pole seen on gross examination (×5·5).* (B) *Melanoma consisting of spindle A and spindle B cells. (Haematoxylin and eosin, ×265).*

Pathological examination. A small pigmented tumour was present arising from the choroid in the posterior pole above the optic disc. It measured 4½ mm in largest diameter and 3 mm in elevation (Fig. 5A). The surrounding retina was detached. There was no gross extrascleral or optic nerve extension.

Histologically the tumour was composed of a mixture of spindle A and spindle B type cells (Fig. 5B). No epithelioid cells were seen and Bruch's membrane was not ruptured. There were a minimal number of chronic inflammatory cells. A shallow detachment involving the macula was present. Degeneration of photoreceptors and outer nuclear layer of the retina was seen overlying the tumour. There was superficial involvement of sclera by tumour cells. The anterior segment was normal.

CASE 3

This 35-year-old woman presented in her fifth month of pregnancy in July 1956 with a history of blurred vision OD for 2 weeks. She had no previous ocular problems. Her best corrected visual acuity was 20/70–2 OD and 20/20 OS. Applanation intraocular pressures were 17 mmHg OU. Fundus examination revealed an elevated mass inferior to the macula 3 to 4 disc diameters in its widest dimension. There was macular oedema and a retinal detachment overlying the mass. The left eye was normal. She was seen at the MEEI and consultants agreed that the lesion was a malignant melanoma. The right eye was enucleated on 21 August 1956.

She was delivered of a normal daughter on 17 November 1956. Since then she and her daughter have remained in good health with no systemic problems.

Pathological examination. A minimally pigmented choroidal tumour 6 mm in largest diameter and 2 mm in height was located in the posterior pole involving the macula. The cell type was classified as spindle B in a fascicular arrangement. Compact spindle cells were present at the base of the tumour. Bruch's membrane was not ruptured. There was minimal invasion of the inner aspect of the sclera.

CASE 4

This 22-year-old woman presented in September 1969 when she was 6 months pregnant with a 4-day history of blurred vision OS. She had no significant past ocular history. Her family history was significant for cancer; her sister died from a central nervous system malignancy at age 16 and a paternal uncle was treated for cutaneous malignant melanoma. Her visual acuity was 20/15 OD and 20/400 OS. Applanation intraocular pressures were 16 mmHg OU. A choroidal tumour was seen inferotemporally in the left eye extending from the ora to posterior to the equator with a retinal detachment at the edges of the tumour. Examination of the fundus OD was normal. Consultants agreed that this was a malignant melanoma OS. The left eye was enucleated on 22 September 1969.

She was delivered of a full-term baby in December 1969. Three and a half years later she developed a carcinoma in situ of the cervix and underwent a total hysterectomy in May 1973. Slides of the cervical lesion have been reviewed and the diagnosis has been confirmed by the authors. In November 1974, she noticed multiple nodules in her right breast which were biopsied and subsequently verified by the authors as metastatic malignant melanoma of mixed cell type. Chemotherapy and BCG therapy were started in June 1975. A liver scan was suspicious for early metastatic disease. In September 1976 she developed multiple bone metastases, which were treated with radiotherapy. She later developed extensive subcutaneous melanotic nodules. Bone marrow failure developed due to extensive chemotherapy. She died on 30 April 1977 of metastatic malignant melanoma and bone marrow failure.

Pathological examination. A tumour 14 mm in largest diameter and 7 mm in elevation was present arising from the choroid. Histologically the tumour consisted almost exclusively of spindle B cells arranged in a fascicular pattern. It was lightly pigmented with minimal chronic inflammation. A retinal detachment was present overlying and surrounding the tumour. The pigment epithelium over the lesion had undergone fibrous metaplasia. Bruch's membrane was ruptured and there was invasion of the overlying retina. No tumour cells were seen in the vitreous. There was invasion of the inner aspect of the sclera but no invasion into the scleral emissary canals.

CASE 5

This 29-year-old nurse presented at the MEEI when 4 months pregnant on 25 July 1961. Her visual acuity was 20/20 OD and no light perception OS. Her right

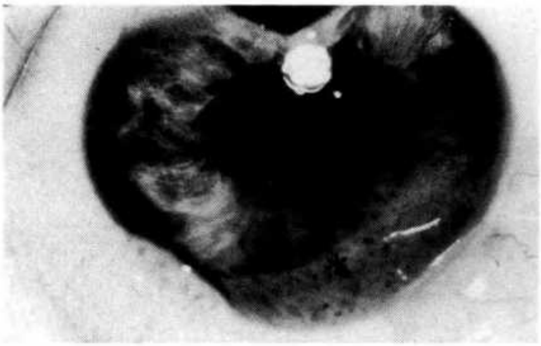

Fig. 6 *Case 5. Tumour involving the iris OS (asterisk).*

eye was normal. Her left eye had minimal conjunctival injection. She had a superior peripheral iridectomy OS. A pale vascularised mass was present on the anterior surface of the iris inferiorly (Fig. 6). There was also a subconjunctival mass at the limbus inferiorly. The pupil OS was irregular, and the anterior chamber was normal in depth. The lens OS had pigment on the capsule. Intraocular pressures were 16 mmHg OD and 38 mmHg OS. The disc OS was atrophic. No masses were seen on dilated fundus examination.

The patient's previous ocular history according to notes obtained in 1961 from her ophthalmologist revealed a normal examination in November 1948, when she was 17 years old. Examination one year later revealed advanced glaucoma OS with optic atrophy and 'marked nasal field loss.' She had an 'iridectomy and sclerectomy' for control of the pressure on 24 April 1950. We were unable to obtain slides of material removed at that time. A cystic, vascularised subconjunctival nodule below the limbus was noted prior to the surgery but not biopsied or resected. No iris lesion was noted at that time. She was followed up by her ophthalmologist over the following years, but these records could not be obtained. An iris lesion had never been mentioned to the patient. Because of the presence of a tumour in her blind eye when seen at MEEI, an enucleation was performed on 11 October 1961.

She was delivered of her child by caesarian section on 26 December 1961. Since then she has had two more caesarian sections and a hysterectomy. During abdominal surgery, exploration for metastases was done which was negative. She has had no further medical problems.

Pathological examination. A tumour consisting mostly of spindle B cells was present, replacing the inferior aspect of the iris and involving the ciliary body and the trabecular meshwork. It extended through the sclera into the subconjunctival space. Tumour cells were present within the inner layers of the corneal periphery and beneath the corneal epithelium at the limbus. Many large vascular channels were present in the tumour. Pigment clumps were scattered among the tumour cells. The angle was closed inferiorly. The choroid showed no evidence of tumour. Diagnosis was malignant melanoma of the spindle B cell type, involving the iris and ciliary body with extraocular extension.

STATISTICAL ANALYSIS

From 1953 to 1973 there were 27 females and 18 males 44 years of age or younger who had an enucleation for uveal melanoma and pathology examination at the Massachusetts Eye and Ear Infirmary with adequate follow-up. In 1980 there were 6 females and 2 males in the same age range. The female to male ratios were 1·5:1 and 3:1 respectively.

The expected number of pregnancies among women 44 years of age or younger in our sample was 2·1. Although the observed number (5) was greater than the expected (2·1), this difference was not statistically significant (one sided p value = 0·06).

OESTROGEN RECEPTOR ANALYSIS

A summary of the findings can be found in Table 2.

Table 2 *^{3}H oestradiol binding in uveal melanoma and choroidal tissue*

Patient (accession number)	*Age*	*Sex*	*Race*	*Tissue*	*Wet weight (mg)*	*Assay protein (mg/ml)*	*Specific binding*
1 (E80–923)	27	F	W	Melanoma	116	1·44	0
6 (B80–1284)	85	M	W	Melanoma,	110	3·74	0
				choroid	25	0·40	0
7 (E80–1334)	54	M	W	Melanoma,	80	3·27	0
				choroid	43	0·46	0
8 (E80–1430)	40	M	W	Melanoma,	80	3·87	0
				choroid	10	–	–
9 (E80–1439)	85	F	W	Melanoma,	80	4·38	0
				choroid	35	–	–
10 (E81–25)	65	M	W	Melanoma,	100	2·15	0
				choroid	110	2·68	0
11 (E81–104)	83	M	W	Melanoma,	120	2·32	0
				choroid	140	2·96	0

One of the specimens studied was a melanoma from a pregnant woman (case 1) in which no oestrogen receptor was detected. The remaining uveal melanomas and normal choroidal tissues that were studied were also negative.

Discussion

It is difficult to ascertain the natural history of melanomas prior to their discovery. In case 1, however, there is no question that her symptoms of discomfort and injection began during the latter half of each of her two pregnancies and that the melanoma grew to ultimately surround the optic nerve while she was pregnant. Reasons for her ocular pain and oedema at similar times during her pregnancy remain speculative but may be related to growth of the melanoma. The decrease in sub-retinal fluid and change in the appearance of the edges of the mass suggested a remission or regression between pregnancies.[36] This case and the others discussed in this report led us to question a possible influence of hormones or other mechanisms involved in pregnancy and the premenopausal period. This hypothesis is corroborated by our finding of an increased female to male ratio in cases 44 years of age or younger. We also found a higher than expected number of pregnancies among women of childbearing age in our sample; however, this was not statistically significant. Since our patients are not necessarily representative of all cases of uveal melanoma in the source population, and the sample size is small, results are suggestive and warrant further investigation.

The present study represents the first investigation in the literature for the presence of oestrogen receptors in ocular melanoma and choroidal tissue. Oestrogen receptors were not found, suggesting that oestrogen receptor activity may not be involved in the presentation or growth of ocular melanomas. This assumption is consistent with the finding that cutaneous melanomas show a poor response to endocrine therapy[37] and that the putative responses to hormone therapy in cutaneous melanoma have no correlation with the presence of receptor.[38] Our receptor test group was small, with only one a melanoma of pregnancy, so a larger number of this relatively rare condition needs to be examined before the statistical significance of the findings can be established. Questions that remain unanswered include: are uveal melanomas of pregnancy different from tumours in nonpregnant age-matched cases with respect to receptor frequency and concentration? Are there significant receptor differences between males and females, and do values change with age?

The absence of oestrogen receptor, however, does not rule out the possibility that oestrogens may influence tissue by a mechanism not involving a receptor, or that they may exert an indirect effect via the regulation of other hormones or factors that directly affect the melanoma. Other possibilities for hormone control other than oestrogens include a direct effect of melanocyte stimulating hormone,[39] androgens,[1] or other trophic factors.

Another possible mechanism is that pregnancy may be associated with decrease of a systemic inhibitor allowing stimulation of growth. An immunological rather than hormonal mechanism consistent with this theory is the recent evidence that fetal suppressor cells are present which affect maternal adult lymphocytes and alter the mother's immunological reactivity, preventing rejection of the fetal allograft.[40] Moreover proteins produced by the mother[41] or a reduction in levels of maternal helper T cells[42] may partly explain survival of the fetus. Changes in cellular and humoral immunity[43 44] occur during pregnancy and are thought to be responsible for the diminution during pregnancy of such autoimmune diseases as systemic lupus erythematosus or rheumatoid arthritis. Pregnancy has also been found to exert a beneficial effect on the Vogt-Koyanagi-Harada syndrome.[45] Similarly, perhaps an increase in immunosuppression-related problems could occur which, for example, would allow development or growth of a pre-existing slow growing melanoma in the eye. Immunodeficiency states are associated with an increased incidence of neoplasia,[46] but this has not been explored in the pregnant state.

To evoke an immunological mechanism there should be evidence that melanoma is an antigenic tumour. Virus-induced tumours are almost always antigenic, and there is suggestive evidence that at least some ocular melanomas contain virus.[47] Moreover, evidence of immunological effects in melanoma patients has been demonstrated.[48]

Our clinical observations pose the following questions: (1) Do pregnancy and other hormonal changes influence the occurrence of uveal melanomas? (2) Does pregnancy affect the course and prognosis of uveal melanomas, and if so, by what mechanism? A case control study would be helpful in answering these questions. Ideally, a prospective follow-up of melanoma patients in a national registry would be established to determine differences in occurrence as well as outcome in women of differing hormonal status controlling for histological and other prognostic factors. Such investigations may provide insight into the patho-physiology or therapeutic management of a subset of patients with ocular melanoma.

We thank Dr Philip Lavin for his suggestions concerning the statistical analysis and Ingrid Von Saltza for her help with translations. Also we would like to thank JoAnne Taschler and Diane Mahoney for helping to prepare this manuscript.

This study was supported in part by Research Grant 1 F32 EY05507-01 from the National Eye Institute (Dr Seddon).

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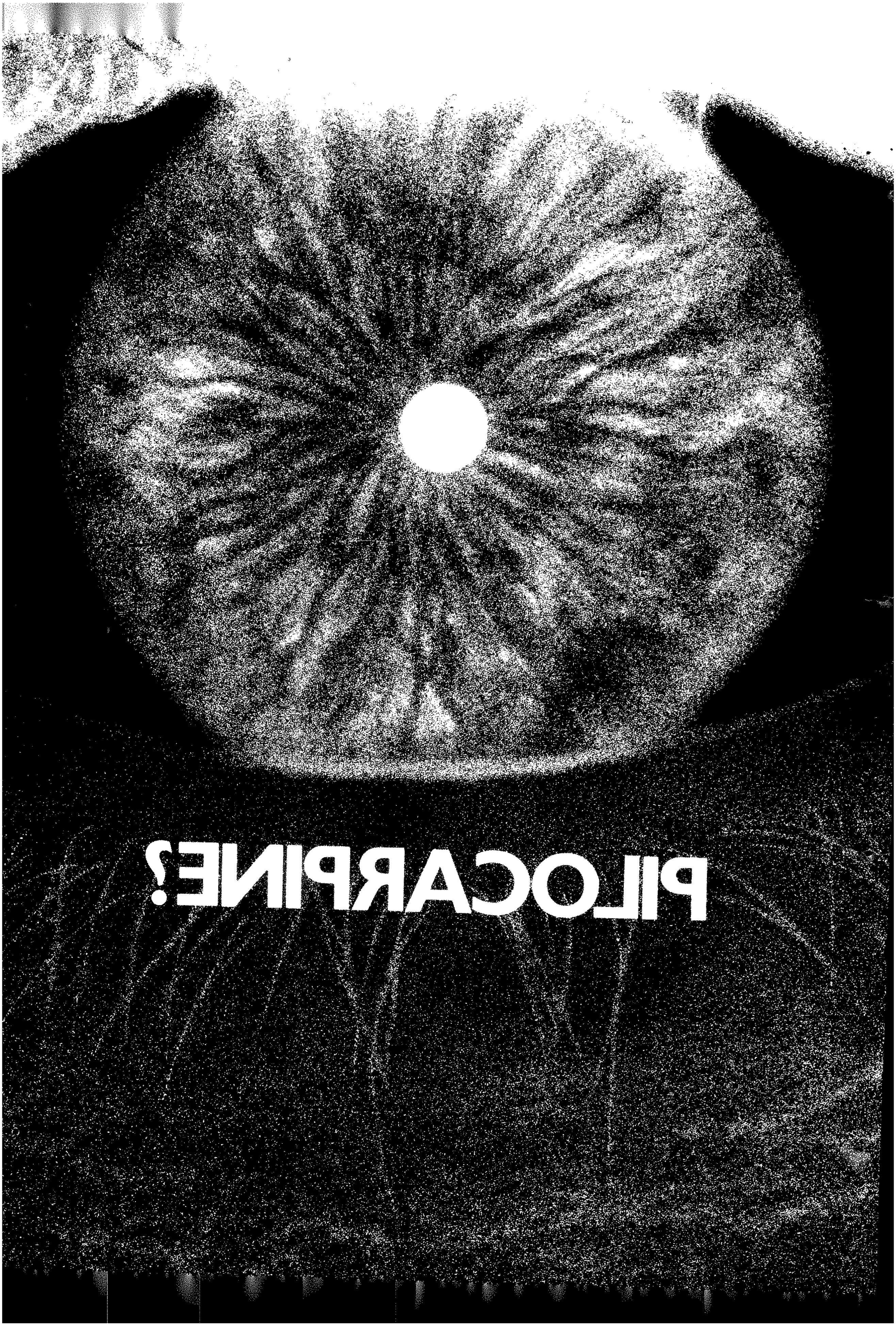
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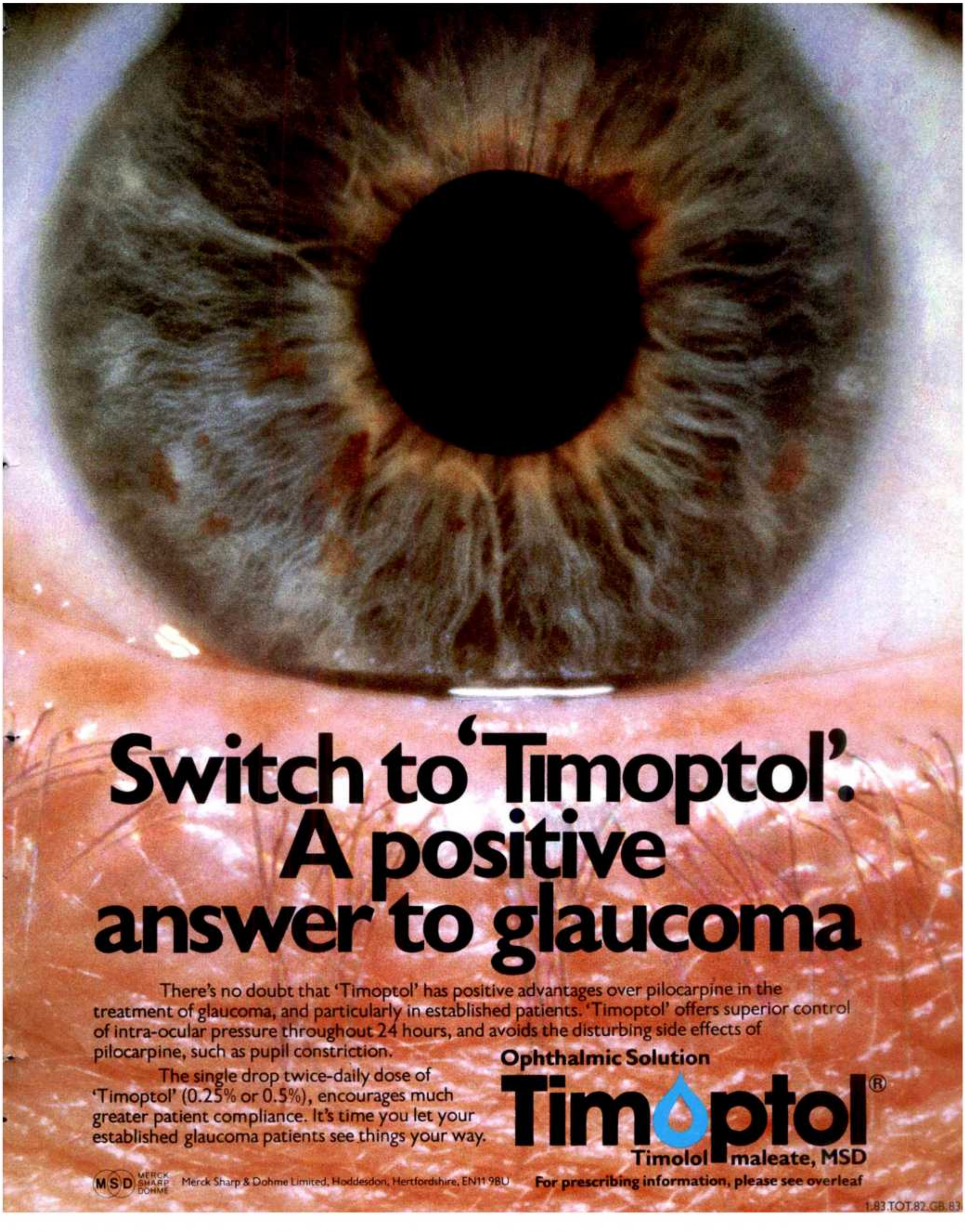

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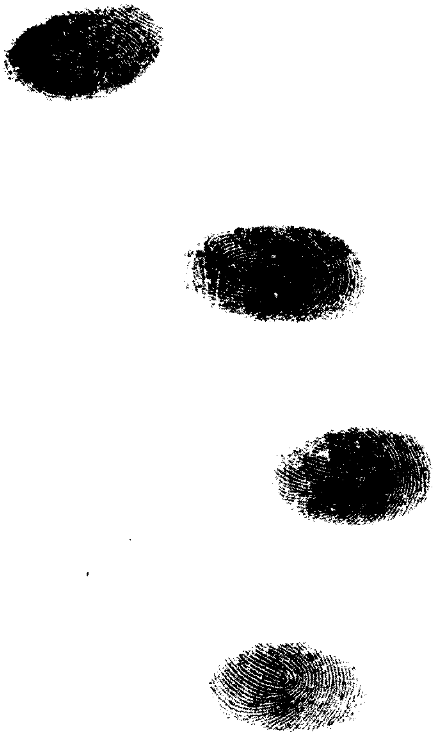

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British Journal of Ophthalmology, 1982, **66**, 705–708

Corticosteroids and corneal epithelial wound healing

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SUMMARY The effect of corticosteroids on the re-epithelialisation of corneas from which the epithelium was removed has been determined by fluorescein staining, photography, and light microscopy. Our results suggest that hydroxymethyl progesterone 1·05% ($p<0·05$), prednisolone 1·0% ($p<0·001$), and dexamethasone 0·1% ($p<0·001$) administered 6 times a day retard the epithelial wound healing compared with control animals which received isotonic NaCl.

The effect of corticosteroids on the corneal epithelium is important for a number of reasons. Corticosteroids are the most effective drugs for the nonspecific suppression of inflammation.[1] They prevent corneal neovascularisation in clinical and experimental work[2 3] and are widely used in current ophthalmology. Finally the integrity[4] and healthy quality[5] of the corneal epithelium are essential to the health of the cornea. Anti-inflammatory steroids may delay the healing of corneal stromal wounds,[6 7] produce glaucoma,[8] and increase the liability to infection.[9 10]

This paper reports experimental results of the effects of different corticosteroids on the healing of rabbit corneal epithelium.

Material and methods

Experimental animals. Twenty pigmented rabbits of both sexes weighing 2 to 3 kg each were used in this study. Each animal was examined in a slit-lamp microscope and no evident pathological findings were noted prior to the experiment.

Epithelial healing study. Forty eyes were divided in 4 groups of 10: Group A received topical isotonic NaCl solution used as control; group B received topical commercial hydroxymethyl progesterone 1·05% solution (Medrysone); group C received topical commercial prednisolone sodium phosphate 1·0% solution (Solucort); group D received topical commercial dexamethasone sodium phosphate 0·1% solution (Decadron phosphate). All these drugs were given 6 times a day.

The method described by Moses *et al.*[11] was used for removal of the corneal epithelium. Our tube has an internal diameter of 7·3 mm at the tip.

Rabbits were anaesthetised with sodium pentobarbital administered in a marginal ear vein (25 mg per kg body weight). Two drops of Novesine (oxybyprocaine hydrochlorate 0·4%) were instilled into each eye. Each eye was then gently proptosed, and the lip of the iodine tube was wiped on a filter paper and held against the cornea for 3·5 minutes. Recording of the lesion was by photography. The cornea was stained with one drop of 0·5% fluorescein (without preservatives) and then washed with 2 drops of isotonic NaCl solution. The lesions were photographed on Kodak Tri-X film 4 times a day until the complete healing of the corneal epithelial wound, which was determined by the absence of corneal fluorescein uptake. An annular electronic flash covered with a Wratten 47 B filter was fixed round the objective of a slit-lamp, and the objective was covered with a Wratten 12 filter to obtain a good contrast on black-and-white films.

With a Quantimet 720 (Cambridge Instruments, UK) the fluorescein-stained areas were measured and converted to square millimeters.

For each eye a healing curve was obtained by plotting successive areas of the wound against time. The best fitting curve by the least squares method was obtained by means of a linear regression.

The diameter of the first corneal wound for each eye was also measured at 6 hours.

Histological study. Four days after treatment 4 eyes from each group were enucleated, stained with haematoxylin and eosin, and prepared for histological examination.

Under the microscope we counted the total number of cellular nuclei on the 4 specimens on a 0·35 mm

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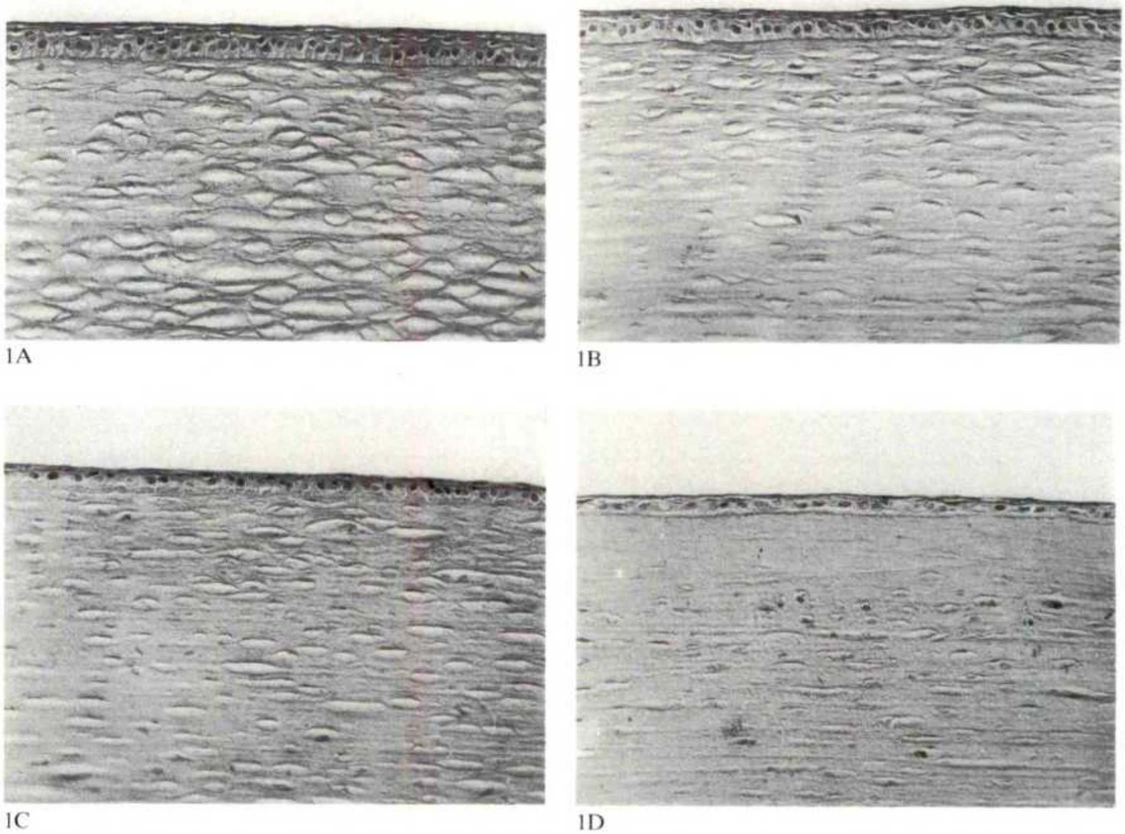

Figs. 1A, B, C, D *Histological cross-sections of healed epithelium after 4 days of treatment. (×622).* A: *Top left, control cornea.* B: *Top right, cornea treated by hydroxymethyl progesterone.* C: *Left cornea treated by prednisolone 0·1%.* D: *Right cornea treated by dexamethasone 1·0%. Note the difference appearing: in the cellular aspect; in the number of layers; in the cellular nuclei.*

length of object. Six different levels of the same paraffin block were studied. These measures were taken on 3 different sectors of the same cornea in a central zone of 4 mm radius.

Results

The mean diameter of the epithelial corneal wounds at 6 hours for each group ranged from 7·85 to 7·71 mn (Table 1). By Student's *t* test the difference was not statistically significant, $p>0{\cdot}05$. Table 2 gives the slopes computed by the least squares linear regression method for all the 40 healing rates individually. The mean rates for each group are also shown.

As shown in Table 2, the difference between the saline-treated group A and the others groups was statistically significant (student's *t* test) at the level $p<0{\cdot}05$ for group B and $p<0{\cdot}001$ for groups C and D.

Table 3 shows the mean number of cellular nuclei on a 0·35 mm length for each group. There was no statistically significant difference ($p>0{\cdot}05$) between the control group A and group B. There is a statistically significant difference ($p<0{\cdot}001$) between group A and groups C and D.

In the control group the anterior epithelium was 3 to 4 layers thick; the basal layer was formed by tall

Table 1 *Mean diameter (mm) ± standard deviation of ulcers at 6 hours*

Group A	*Group B*	*Group C*	*Group D*
$m_1=7{\cdot}64\pm0{\cdot}35$ —	$m_2=7{\cdot}69\pm0{\cdot}25$ $p>0{\cdot}05$	$m_3=7{\cdot}58\pm0{\cdot}20$ $p>0{\cdot}05$	$m_4=7{\cdot}71\pm0{\cdot}32$ $p>0{\cdot}05$

Table 2 *Rate of decrease of area of epithelial wound (mm²/h)*

Group A Control	*Group B Hydroxymethyl progesterone 1·05%*	*Group C Prednisolone 1·0%*	*Group D Dexamethasone 0·1%*
1·25	1·06	0·74	0·48
1·07	1·11	0·60	0·74
1·15	1·08	0·53	0·52
1·14	1·05	0·82	0·53
1·32	0·98	0·61	0·48
1·08	0·85	0·54	0·42
1·13	1·15	0·53	0·54
1·02	1·05	0·81	0·61
1·17	0·89	0·62	0·75
1·40	0·99	0·87	0·87
α $m_1=1·17\pm0·12$	$m_2=1·02\pm0·09$	$m_3=0·67\pm0·13$	$m_4=0·59\pm0·15$
β —	$p<0·05$	$p<0·001$	$p<0·001$

Each value listed presents the healing rate obtained from an animal.
α=Mean healing rate±standard deviation.
β=p values.

Table 3 *Mean number of cellular nuclei±standard deviation per 0·35 mm on histological preparation*

Group A	*Group B*	*Group C*	*Group D*
$m_1=73·20\pm8·81$	$m_2=69·25\pm10·30$	$m_3=41·10\pm7·80$	$m_4=44·21\pm7·10$
—	$p>0·05$	$p<0·001$	$p<0·001$

polyhedral cells with no apparent histological lesions (Fig. 1A). The epithelium in the group B specimen did not differ much from that of the control group. There were only a few foci where the upper epithelial layers consisted of flattened parakeratotic cells (Fig. 1B).

In contrast, the epithelium of groups C and D was one or 2 layers thick. The cells of the basal layer seemed to have lost their junctional units, and the superficial layers were formed of extremely flattened cells with hyperchromatic nuclei (Figs. 1C, D). The histological study was restricted to the centre of the lesion.

Discussion

There are certain conditions in which, despite a break in the corneal epithelium, we are obliged to administer topical corticosteroids. In order to obtain information on the epithelial regeneration of the cornea when treated with different corticosteroids the healing process of a superficial epithelial corneal ulcer was measured. Histological studies have been performed to evaluate the quality of the regenerated epithelium. For the removal of the corneal epithelium we used a reproducible method[11] which respects[12] the epithelial basal membrane.

Our results suggest that topical application of prednisolone 1·0% and dexamethasone 0·1% 6 times a day decreases ($p<0·001$) the epithelial healing rates in comparison with those of the control group. Hydroxymethyl progesterone also produces a slight ($p<0·05$) retardation in the epithelial wound healing. There is a statistically significant difference at the 0·001 level between the mean healing rates of group B (hydroxymethyl progesterone) and groups C (prednisolone) and D (dexamethasone).

Our results are confirmed by the histological study. The total number of cellular nuclei was reduced ($p<0·001$) for the groups C and D and histological alterations have been observed. The number of cellular nuclei in group B did not differ from that of the control group, and the histological appearance in both groups was almost the same.

In agreement with our results Aquavella *et al.*[7] reported that in epithelial abrasions the retardation of healing observed after prednisolone treatment was statistically significant but transient in nature. They suggested that this effect is clinically unimportant.

Ho and Elliot[13] found that topical application of 16 drops per day of vehicle or dexamethasone sodium phosphate (Decadron) decreased the epithelial healing rate when compared with saline drops administered 4 times daily. They suggested that the frequent instillation of the drops and not the contents may produce this effect. The vehicle used, containing 0·2% benzalkonium chloride, is toxic[14 15] to the epithelium at this concentration.

Recently Srinivasan and Kulkarni[16] demonstrated that 1·0% prednisolone acetate and 0·1% dexamethasone did not affect the course of re-epithelialisation after partial corneal epithelial denudation. On the contrary the healing rate was significantly retarded after complete corneal denudation. We think that the larger diameter of the epithelial denudation used in our method explains the different results obtained. Moreover in this study the drugs were administered 3 times daily.

Epithelial punctate keratitis has also been reported in human corneas after topical application of prednisolone[17] and important morphological changes in the epithelium of rabbit cornea.[18] It has been shown that repeated application of prednisolone 1·0% and dexamethasone 0·1% can retard the epithelial wound healing of a superficial epithelium ulcer.

For hydroxymethyl progesterone, a synthetic corticosteroid which is an effective anti-inflammatory agent for certain external conditions[19] free from the propensity to raise the intraocular pressure,[20] the results in our model proved that the epithelial wound healing was slightly retarded. The purpose of this study was to facilitate recognition of the adverse effect of the corticosteroids and to stress the need for further investigation, both in vivo and in vitro, the effects of these drugs on the corneal epithelium under normal and abnormal epithelial healing.

This study was supported by INSERM U 86 grants.
We thank the Essilor Company for the Automatic Image Analyser.

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British Journal of Ophthalmology, 1982, **66**, 709–713

Rate of endothelial cell loss in the early postoperative period after cataract surgery

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SUMMARY Central corneal endothelial cell density was estimated in 33 consecutive patients preoperatively and at monthly intervals for 6 months after cataract surgery. The patients were divided into 3 groups by a random procedure to have either intracapsular extraction or intracapsular extraction plus Federov 4-loop iris clip lens, or extracapsular extraction with Binkhorst 2-loop iridocapsular lens. In all groups the greatest cell loss had occurred by one month and thereafter no accelerated loss was apparent except in individual patients. The limitations of such a method of assessment are discussed.

Lens implantation has gained in popularity and acceptance in recent years, and over 100 000 lens implants are said to be carried out yearly in the United States. Although the short-term efficacy of lens implantation is not in doubt, there are few reports of long-term follow-up. One of the most serious long-term complications is corneal oedema and bullous keratopathy caused by depletion of endothelial cells.

All intraocular procedures produce some cell loss, and even trivial manoeuvres will cause some endothelial cell drop-out.[1] The early reports of cell loss following lens implantation showed comparatively large amounts of cell loss,[2–4] but refinements in methods and use of closed chamber techniques have greatly reduced cell depletion.[5]

While it is probable that cell loss is mostly caused by mechanical injury at operation,[6] endothelial cells are vulnerable to mild trauma.[7] As it seems likely that a perfect irrigating solution has not yet been found,[8 9] surgery, especially extracapsular surgery, which may require irrigation by comparatively large volumes of fluid, could have a long-term effect on the rate of cell loss.

The purpose of this study was to measure central corneal density before cataract surgery and monthly after the operation in an attempt to determine the rate of cell loss after operation and to see whether this differed between 3 different types of surgery.

Material and methods

Thirty-three patients with uncomplicated senile cataract, already enlisted in a cataract management study, were allocated by a randomisation procedure to have either (1) intracapsular extraction, (2) intracapsular extraction plus Federov 4-loop implant, or (3) extracapsular extraction plus Binkhorst iridocapsular lens implant. In all patients only one eye was operated on, and surgery was carried out by 2 experienced surgeons using standard techniques.

Axial endothelial photographs were obtained with the Nikon noncontact photo-slit camera preoperatively and approximately at monthly intervals for 6 months after surgery. Enlarged prints were made and cell density estimation obtained by the method described previously.[10] The 33 patients were distributed equally between the 3 groups. Patient compliance was good, and of 231 expected sets of photographs 198 were obtained. Missing data were due to: failure of attendance 19; failure to obtain clear photographs 14; total 33.

The mean number of observations per patient was 6, and only one patient had fewer than 4 sets of photographs. We aimed to count 3 photographs per visit, and this was achieved in 66 out of the 198 sets, the remaining counts being based on the best 2 photographs. In a small number of cases only one clear photograph was obtained. These are indicated by an asterisk in the accompanying tables.

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Fig. 1a

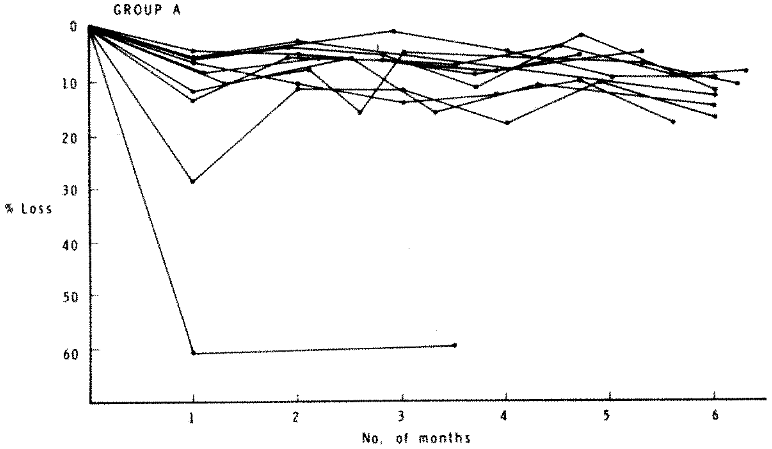

Fig. 1b

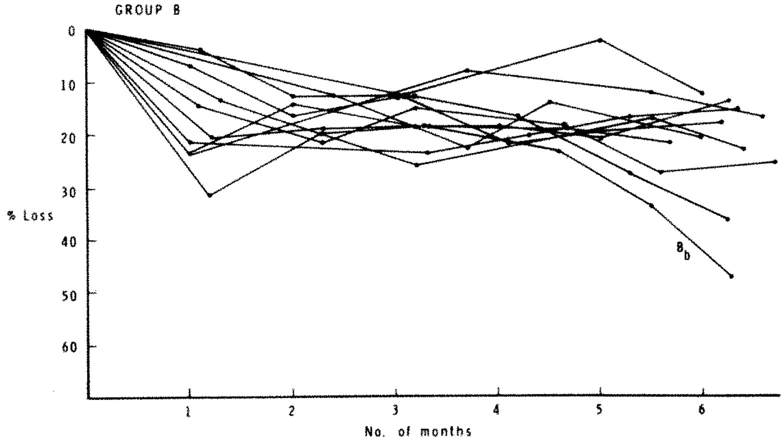

Fig. 1c

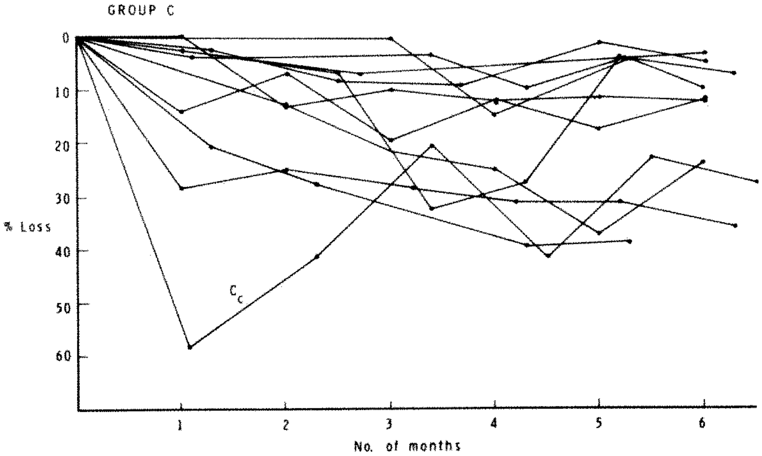

Fig. 1a,b,c *Percentage cell loss with time for 3 different treatment groups (each line represents one patient).*

Results and discussion

The mean axial cell counts for the 3 different treatment groups are shown in Tables 1-3. Each count was expressed as a percentage of the preoperative count for that patient. The percentage loss with time is illustrated by treatment group in Fig. 1. These results illustrate a number of points. Firstly, cell loss appears to be greater after lens implantation, whether after intracapsular extraction or extracapsular extraction, than after intracapsular extraction alone.

Secondly, although there is wider variation in loss between patients in group C than in the other 2 groups, it is not clear whether there is any real difference in the mean cell loss between groups B and C.

Although most patients appear to lose cells, in some patients there is a wide fluctuation in estimates from one month to the next. This is particularly marked in group C (e.g., patient Cc). These fluctuations are too large to be explained by the error inherent in our method of estimation of endothelial cell density. Indeed, if this was the case, one would expect similar fluctuations to be present in all 3 groups.

The most likely cause of the variation is that after operation the cell loss in some patients is unevenly distributed over the cornea. It has been shown[11][12] that in normal eyes endothelial cells are fairly evenly distributed over the cornea even though there may be a small difference in density between the superior and inferior endothelium.[13] Following surgery cell loss may be uneven, so that closely adjacent regions of the cornea may exhibit widely differing endothelial cell densities. An extreme example is illustrated in Fig. 2. Although we aimed to take axial photographs in each case, it is difficult to ensure that exactly the same part of the cornea is photographed on each visit.

To test this hypothesis we selected one patient from each group and took a series of photographs from above downwards and estimated the cell density. The results are shown in Table 4. There is a progressive increase in cell density from top to bottom which is

Table 1 *Group A, intracapsular cataract extraction, mean cell counts*

	Time interval						
Patient	*Preop.*	*1*	*2*	*3*	*4*	*5*	*6*
a	2573 (680)	2420 (40)	2510 (20)	—	—	—	2260 (580)
b	2907 (440)	1120 (200)	—	—	1166 (40)	—	—
c	2530 (100)	2230 (120)	2400 (220)	2140 (260)	2273 (220)	—	2170 (300)
d	2780 (20)	2413 (140)	2633 (120)	2613 (120)	2550 (20)	2680 (40)	—
e	2820 (80)	2670 (60)	2720 (40)	2680 (80)	2520 (40)	2800 (80)	2500 (*)
f	3010 (220)	2706 (240)	2786 (280)	2547 (480)	2880 (240)	2820 (*)	2710 (20)
g	2990 (140)	2830 (140)	—	2987 (100)	2860 (160)	2728 (80)	2727 (227)
h	3310 (20)	3110 (100)	2973 (120)	2860 (0)	2900 (120)	3000 (80)	2730 (220)
i	2920 (0)	2670 (100)	2750 (180)	2730 (60)	2833 (360)	2680 (120)	2700 (200)
j	2710 (140)	2600 (100)	2580 (40)	—	2500 (*)	2600 (80)	—
k	2610 (100)	1870 (20)	2320 (0)	2320 (40)	2147 (20)	2351 (360)	2190 (100)

Figures in brackets indicate the range (i.e., difference between the highest and lowest estimations) on which the mean is based.
*Estimate based on only one count.

Table 2 *Group B, intracapsular cataract extraction plus Federov II implant, mean cell counts*

	Time interval						
Patient	*Preop.*	*1*	*2*	*3*	*4*	*5*	*6*
a	2910 (100)	2220 (40)	—	—	2690 (260)	2580 (120)	2420 (120)
b	2450 (140)	1680 (280)	1970 (180)	2000 (320)	1887 (200)	1620 (80)	1280 (40)
c	2440 (160)	—	2140 (80)	1900 (320)	2107 (180)	—	1930 (60)
d	3427 (360)	2700 (40)	—	2620 (280)	2740 (40)	2870 (100)	2900 (40)
e	1800 (40)	1430 (100)	1460 (160)	1470 (*)	1460 (120)	—	1410 (60)
f	3050 (220)	2606 (340)	2400 (160)	2600 (120)	2490 (180)	2220 (40)	2280 (80)
g	2400 (80)	2240 (60)	2013 (60)	2090 (140)	—	2360 (40)	2120 (200)
h	3180 (*)	—	—	2790 (60)	2500 (0)	2547 (140)	2610 (60)
i	2680 (120)	2327 (140)	—	1990 (60)	—	2230 (100)	2070 (100)
j	2753 (200)	2100 (120)	2370 (100)	2240 (160)	2240 (240)	2180 (40)	2380 (0)
k	2610 (60)	2510 (20)	2290 (20)	2293 (140)	2170 (220)	1890 (140)	1660 (160)

See footnotes to Table 1.

Table 3 *Group C, extracapsular cataract extraction plus iridocapsular implant, mean cell counts*

Patient	*Time interval*						
	Preop.	*1*	*2*	*3*	*4*	*5*	*6*
a	2930 (20)	2860 (40)	2690 (140)	—	2670 (20)	2900 (80)	2800 (200)
b	2930 (140)	2520 (160)	2740 (200)	2353 (180)	2587 (80)	2430 (20)	2587 (100)
c	2390 (100)	987 (80)	1393 (180)	1907 (160)	1393 (200)	1853 (53)	1733 (160)
d	3307 (110)	3310 (20)	2870 (20)	2980 (40)	2920 (120)	2933 (140)	2910 (60)
e	2520 (200)	—	2200 (*)	1973 (400)	1890 (60)	1586 (240)	1930 (100)
f	3460 (340)	2747 (160)	2500 (120)	—	2100 (160)	2133 (200)	—
g	2610 (20)	—	—	2610 (60)	2240 (240)	2510 (20)	2360 (80)
h	2247 (80)	1607 (20)	1680 (*)	1610 (20)	1527 (60)	1527 (20)	1441 (100)
i	2330 (100)	2270 (20)	—	2173 (100)	—	—	2268 (0)
j	2807 (160)	2740 (200)	2633 (320)	1900 (180)	2033 (40)	2710 (300)	—
k	2840 (40)	2740 (*)	—	2750 (220)	2580 (160)	2730 (140)	2650 (20)

See footnotes to Table 1.

consistent with the findings of Hoffer[12] for cataract patients. The differences detected are great enough to explain the intrapatient fluctuations. When these fluctuations are taken into account, it appears that most of the cell loss occurs soon after surgery, probably within the first month. There is no clear evidence of continuing cell loss except in the case of one patient, Bb. This was the only case in this series with a major complication. The wound opened 3 weeks after surgery, with loss of the anterior chamber and prolonged contact of the implant with the endothelium. Although this was satisfactorily repaired and the anterior chamber reformed, this patient has continued to lose cells at a rapid rate. The reason for this is not clear.

Table 4 *Cell density in 3 eyes: in descending order vertically from top to bottom of cornea. Top=midway from centre to upper limbus at 12 o'clock; bottom=lowest picture between centre and limbus at 6 o'clock*

	Patient Ah in group A	*Patient Bb in group B*	*Patient Cc in group C*
Top	1920	426	880
	2120	439	980
	2980	466	920
	2980	519	1140
Middle	2920	453	1440
	2840	519	1740
	2900	453	1660
	2880	466	2400
	3000	439	
Bottom	2880	466	

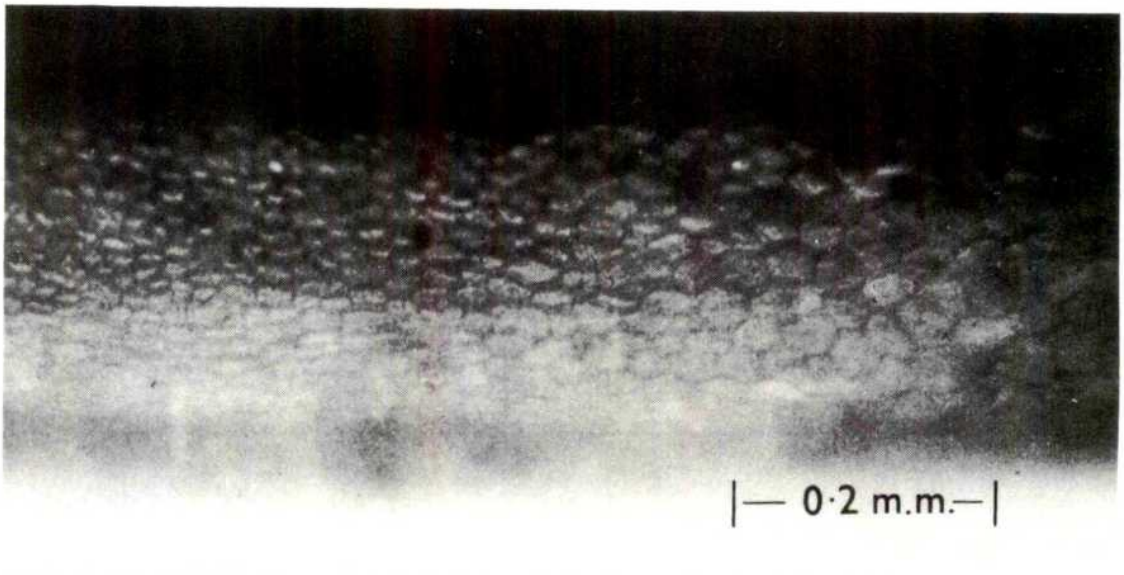

Fig. 2 *Axial endothelial cell photograph from a patient following intracapsular cataract extraction, to illustrate variation in endothelial cell density within a short distance across the cornea.*

CONCLUSIONS

The fluctuations in cell counts from month to month shown by some patients illustrate one of the difficulties of obtaining meaningful estimates of endothelial cell density. Evidence based on only one postoperative count should be interpreted with caution.

Our data also indicate that most cell loss occurs within the first month after surgery. This emphasises the importance of good technique to avoid endothelial cell damage at the time of surgery. Whether there is continuing cell loss over a longer period, or whether there is a difference in cell loss with different types of extraction and lens implant, are important questions that are not answered by the present study. With longer follow-up of larger groups of patients this information should become available.

We are grateful to Mr D. Barbour for photographic assistance and Mrs M. Platts for secretarial help.

This paper is supported by the National Institutes of Health, USA grant no. EYO 2677-03.

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British Journal of Ophthalmology, 1982, **66**, 714–716

Complications from use of sodium hyaluronate (Healonid) in anterior segment surgery

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SUMMARY Sodium hyaluronate brings an important new advance to several techniques in ophthalmic microsurgery. Its use in 226 primary lens implantations is described, and it has been found to be safe and beneficial to both surgeon and patient. Apart from a one day rise of intraocular pressure, obviated by the routine use of timolol maleate or acetazolamide, it has been found in the dosage used to be free from complication.

Sodium hyaluronate was first used in ophthalmic surgery as a vitreous substitute more than 10 years ago[1] when its properties were shown to be elastic, highly viscous, yet nontoxic, noninflammatory, and nonantigenic.[2] More recently Balazs, Miller, and Stegmann introduced its use into anterior segment surgery.[3-5] The 1% solution (Pharmacia UK Ltd, Healonid) is at least 400 000 times more viscous than aqueous yet will pass through the fine Rycroft cannula. It is totally transparent, and because of its high molecular weight it is nonosmotic. Because of these properties and the fact that it will maintain anterior chamber depth when air may not, it has been described as the ideal medium for closed chamber surgery.[6]

The particular assets of Healonid are that it will allow complex surgical manipulation in the anterior chamber, improving visibility while protecting the corneal endothelium and surrounding tissues from the trauma of surgical instrumentation. It may also be used to aid atraumatically the cleavage of iris synechiae or other adherent tissues. Thus Healonid has a place in the field of trauma[7,8] (synechiolysis, extraction of corneal splinters penetrating the anterior chamber, anterior segment reconstruction), in keratoplasty[4,5,9] (both for donor and recipient eye to protect endothelium), in filtration surgery[5] (to prevent flat anterior chamber and hypotonia), in extracapsular cataract extraction[5,6] (during capsulectomy and to protect endothelium from a hard lens nucleus), and in the field of lens implantation[4-6,9-13] (anterior chamber manipulation, protection of endothelium, synechiolysis, iris suturing, and to maintain anterior chamber depth for secondary procedures such as keratoplasty and filtration surgery). Healonid may also be used in retinal detachment surgery[14,15] (for internal tamponade).

This communication seeks to assess the possible complications that may be attributed to Healonid in the field of primary lens implantation.

Material and methods

Three hundred and thirty-four consecutive lens replacements were performed during the 29 months commencing January 1980. 244 followed planned extracapsular nucleus extraction (as described previously[6]) with an age range 39–88, mean 73 years; 90 followed intracapsular cryoextraction after zonulysis, with an age range 56–94, mean 77 years. Healonid was used for every case when it was available. For standardisation, between 0·2 ml and 0·3 ml was used per eye whether or not the particular eye needed it. There was therefore no patient selection for the use of Healonid. No attempts were made to aspirate Healonid at the end of surgery. It was used in a total of 226 eyes to deepen the anterior chamber prior to lens implantation. Of these, 164 followed extracapsular extraction when it was also used to maintain the anterior chamber during capsulectomy and inserted to provide a cushion between lens nucleus and cornea during extraction, and 62 followed cryoextraction, 46 of which also necessitated an iris suture, placed as described by the author[12]

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Table 1 *Postoperative ocular hypertension in 334 eyes*

Eyes	*First day*		*Mean IOP (mmHg)*	
	IOP>30 mmHg	5 mm>preop.	1st day	3rd day
108 Controls	11 (10%)	24 (22%)	18·9	15·7
54 Healonid	17 (31%)**	31 (57%)**	25·6	15·5
109 Healonid+acetazolamide	8 (7%)**	38 (35%)*	19·7	14·4
63 Healonid+timolol	7 (11%)*	20 (32%)*	20·0	14·2

IOP=intraocular pressure.
*p<0·01; **p<0·001.

under Healonid with the chamber closed. There was only one case of aborted lens implantation during the 29 months, this being for reasons of vitreous loss.

Postoperative routine included careful slit-lamp examination by the author on the first, third, and fifteenth postoperative days and more frequently when necessary. Raised intraocular pressure was treated with topical timolol maleate or systemic acetazolamide or both in combination. However, following the initial trial with 54 cases, in order to obviate further ocular hypertension, 2 subgroups of patients receiving Healonid were made: (*a*) during 1981 109 patients were given routine intramuscular acetazolamide 500 mg 4 hours after completion of surgery followed by tablets 250 mg q.d.s. for 2 days; (*b*) during 1982 63 eyes received timolol maleate 0·25% drops on completion of surgery followed by b.d. application for 2 days. Particular attention was paid to development of uveitis, wound healing, and ocular hypertension.

POSTOPERATIVE OCULAR HYPERTENSION

Healonid leaves the anterior chamber by way of the aqueous outflow channels,[16] but the viscosity has to be reduced by dilution with aqueous before this hydrophilic substance may run through the trabecular meshwork. Intraocular pressure may rise therefore if excessive amounts of Healonid remain in the anterior chamber at the end of surgery.

One hundred and eight eyes did not receive Healonid or any routine ocular hypotensive. These acted as controls (Table 1). Of 54 eyes initially receiving Healonid (all were extracapsular extractions) 57% showed a rise of intraocular pressure 5 mm or more than the preoperative level. The first day applanation was over 30 mmHg in 31% and the mean intraocular pressure was 25·6 mmHg compared with 18·9 mmHg in the control group.

Results

In a double-blind trial on 21 normal subjects guttae timolol 0·5% has been shown to reduce the aqueous flow by 33% and tab. acetazolamide 250 mg by 27%.[17] Of the 109 eyes in the present study receiving Healonid and routine postoperative acetazolamide the mean first-day intraocular pressure was 19·7 mmHg, and only 7% of readings were over 30 mmHg. Of the 63 eyes receiving Healonid and routine timolol the corresponding figures were 20·0 and 11% respectively.

These findings confirm the value of acetazolamide and timolol in reducing aqueous secretion, and Table 1 also shows that by the third postoperative day there was little difference in mean intraocular pressure between the different groups, the marginally higher mean pressure found in controls being explained by the fact that these eyes were less likely to have been offered treatment.

No significant difference was found between intracapsular and extracapsular eyes (Table 2). There were no cases of pupil block glaucoma among the groups receiving Healonid.

Discussion

UVEITIS

On the first day slit-lamp examination often gives the appearance of a plastic anterior uveitis in an eye containing Healonid. However, this is due to the presence of Healonid holding cells in suspension. Flecks of blood may also be seen held in suspension due to rouleaux caused by altered electrostatic charge on red blood cells. These appearances vanish by the third day and do not require specific treatment. 7% of

Table 2 *Incidence of raised intraocular pressure on first postoperative day (the initial 54 extracapsular eyes receiving Healonid are excluded)*

		IOP>30 mmHg	*5 mm>preop.*
Controls	28 IC	3 (11%)	5 (18%)
	80 EC	8 (10%)	19 (24%)
Healonid	62 IC	6 (10%)	26 (42%)
	110 EC	9 (8%)	31 (28%)

IOP=intraocular pressure. IC=intracapsular. EC=extracapsular.

Healonid eyes and 8% of controls were recorded as having a more severe uveitis than is expected during the first postoperative week, but there were no cases of hypopyon or of developing keratic precipitates. There were no cases of spluttering hyphaema or of the uveitis-glaucoma-hyphaema (UGH) syndrome.

WOUND HEALING

There were no eyes in which delayed healing or improper apposition could be attributed to Healonid. A disadvantage of Healonid is that at the end of surgery it is more difficult to assess whether a wound is water-tight than when the anterior chamber is reconstituted purely with salt solution. This is of particular importance during keratoplasty,[9] and alternative methods of reconstituting the anterior chamber should be preferred during the final phases of surgery.

VISUAL ACUITY

After 17 patients had been excluded because of pre-existing visual defects unrelated to cataract all eyes were seeing 6/12 or better at the final point of follow-up except for the following: (i) macular oedema: 5 intracapsular eyes and one extracapsular eye were seeing 6/18 or less, 4 had received Healonid and two had not; (ii) retinal detachment: one intracapsular eye; (iii) corneal decompensation: one extracapsular eye that had not received Healonid.

CONCLUSION

The use of sodium hyaluronate is perhaps the single most important advance to be seen in anterior segment surgery in 10 years. It is safe and free from complications except an ocular hypertensive effect, which generally lasts for less than 3 days. This may be obviated by the routine use of postoperative timolol maleate or acetazolamide or both in combination.

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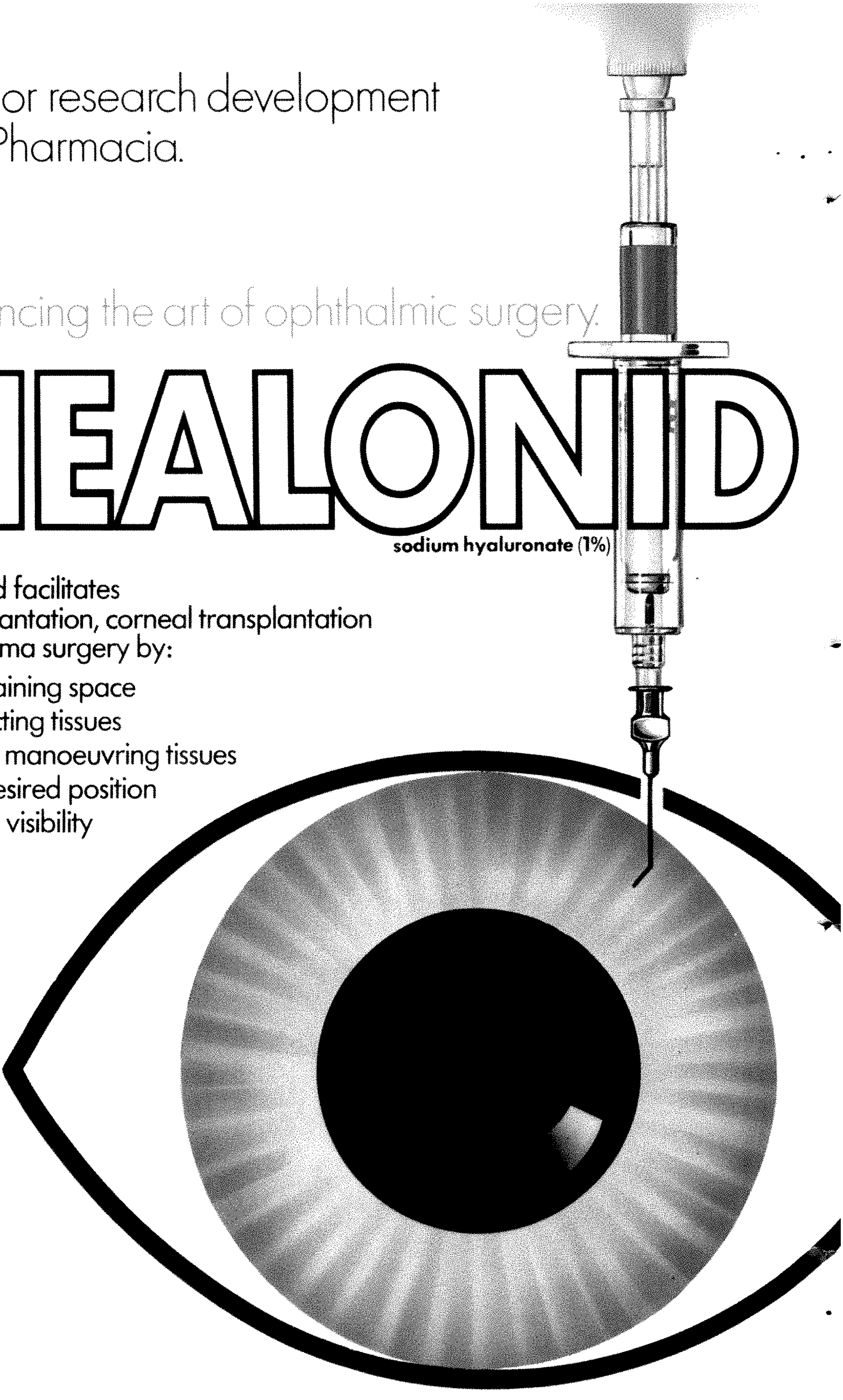

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PRESCRIBING INFORMATION

PRESENTATION

Disposable 0.4 ml syringes containing 1% sodium hyaluronate in aqueous buffer.

USES

Sodium hyaluronate is a visco-elastic polymer normally found in the aqueous and vitreous humour. HEALONID, which contains sodium hyaluronate is a highly viscous clear solution at rest, yet it will readily flow through a fine cannula or needle under pressure. Introduction of HEALONID into the anterior or posterior chamber keeps tissues separated during the operative procedure and protects them from trauma from other tissues or instruments. The anterior chamber depth is maintained, vitreous bulge can be reduced, and the loss of irreplaceable endothelial cells which inevitably accompanies surgery can be greatly reduced.

INDICATIONS

Surgical procedures on the eye, including intraocular lens insertion, intra and extra capsular lens extraction, glaucoma surgery, corneal graft, surgery for accidental trauma, retinal detachment and vitreal replacement procedures.

DOSAGE AND ADMINISTRATION

The syringe is assembled and made ready for use according to the instruction sheet with each syringe.
The indication for use will govern the timing and quantity of HEALONID used. See Data Sheet or HEALONID monograph.

PRECAUTIONS

The anterior chamber should not be over-filled with HEALONID, except in glaucoma surgery. At close of surgery some of the HEALONID should be removed by irrigation or aspiration. Intraocular pressure should be monitored during the post operative period and any excessive rises treated with appropriate therapy.

CONTRA-INDICATIONS, WARNINGS

There are no known contra-indications to HEALONID. Because the drug is extracted from avian tissues, despite rigorous purification procedures minute amounts of protein are present, and thus the remote possibility of idiosyncratic reactions remains.

ADVERSE REACTIONS

The drug is very well tolerated and the only untoward effect reported has been a transient rise in intraocular pressure in a few cases.

PHARMACEUTICAL PRECAUTIONS

Store at 2–8°C protected from light and freezing. Shelf life 3 years.

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FURTHER INFORMATION

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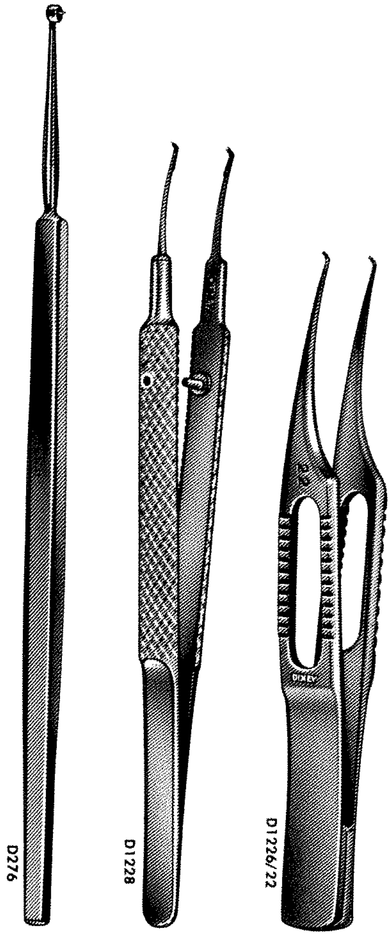

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British Journal of Ophthalmology, 1982, **66**, 717–720

Immunoglobulin patterns in keratoconus with particular reference to total and specific IgE levels

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SUMMARY A selection of sufferers from keratoconus and random controls were assessed in order to substantiate claims that there existed a significant incidence of patients with both keratoconus and a raised serum level of immunoglobulin E. The results appeared to confirm a high incidence of raised total serum IgE levels in patients with keratoconus and also indicated that the additional measurement of serum specific IgE was more sensitive than total IgE. In fact 59% of the patients with keratoconus in our study were identified as having significantly raised levels of specific immunoglobulin E, and 52% were identifiable by measuring total immunoglobulin E. This compares favourably with a previous incidence in a keratoconus population of 47% with raised total immunoglobulin E. Our study avoids clinical estimation of known associated systemic manifestations of atopic disease, thereby reaffirming the correlation between raised serum levels of IgE and keratoconus as objectively as possible. This identification pattern may be useful in reviewing high-risk groups and aid in the earlier detection of the condition.

Keratoconus is an ectasis of central corneal tissue which may also involve the periphery. Presenting in adolescence, the condition is usually self-limiting within 5-10 years, but it can be progressive or undergo an acute relapse often in the fourth decade. If the condition does not become arrested early in its development or shows an acute relapse, the patient may require surgical intervention by means of keratoplasty. On microscopic examination dehiscences are present in Bowman's membrane and the epithelial basement membrane, and the corneal stromal lamellae are reduced in number and attenuated. If Descemet's membrane is breached, acute oedema or corneal hydrops may be established.

Keratoconus has been loosely associated with atopic disease on many occasions.[1-5] More recent reports have substantiated by immunological means the clinical impression that atopic disease, in any of its presentations, was more common in keratoconus.[6 7] The known immunological disturbance associated with atopic disease, namely, raised serum levels of immunoglobulin E, was also shown to exist at a significant level in keratoconus patients.[8] This observation therefore offers the possibility of an immunological marker for keratoconus. Previous studies also gave an indication, though not proved statistically, that there was a more general disturbance of autoimmunity and gammaglobulin status.[9 10] These workers had detected raised IgG and IgM plus selected but nonspecific auto-antibodies in the sera of their keratoconus groups.

An indication of how diverse the results have been can be summarised as follows. On the basis of a clinical estimation of the association between atopic disease and keratoconus the incidence has varied from no correlation up to 35% of keratoconus patients having atopic disease.[8 11 12] The most recent figure of 47% is based not on clinical findings but on the measurement of raised total immunoglobulin E.[8] In this study a highly selective group of keratoconus patients had an incidence of 60% with raised total IgE. These were patients who had both keratoconus and a clinical expression of the atopic state. It was our intention to be entirely unselective on clinical grounds and attempt to gain a high degree of specificity from laboratory investigation alone. A group of keratoconus patients of both preoperative and postoperative types were selected at random from outpatient clinics.

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In addition total and specific IgE levels in a random unselected group of the population were studied for comparison.

Materials and methods

Venepuncture samples were collected from 27 patients, 7 females and 20 males, who were diagnosed as having keratoconus. The clinical diagnosis of keratoconus was made by using the slit-lamp biomicroscope, corneal reflection patterns, and measurement of gross refractive distortion. Many clinics assisted in the collection of samples, and patients were drawn from a large geographic area, including both west and central Scotland.

After separation the samples of sera were stored at −20°C until assay. The immunoglobulins G, A, and M were measured by radial immunodiffusion technique using Behring plates. Total and specific IgE levels were measured by solid-phase radioimmunoassay. Total serum IgE was estimated by the paper radio immuno sorbent test (PRIST) as supplied by Pharmacia. Specific IgE to egg white, milk, fish (cod), house dust mite, cat epithelium, dog dander, and the grass pollen *Poa pratensis* were measured by the radio allergo sorbent technique (RAST) as supplied by Pharmacia.

Autoantibodies against cell nuclei, smooth muscle proteins, and mitochondria were looked for by immunofluorescence tests performed on frozen sections of rat stomach, liver, and kidney. Rheumatoid factor was detected by latex agglutination tests with commercial kits (Wellcome).

Blood samples were also taken from 46 normal unselected adults. The total and specific IgE levels of these control sera were measured to obtain a baseline for the incidence of raised total and specific IgE levels in a control population.

Results

Rahi *et al.*[8] reported increased levels of immunoglobulins G and M in Keratoconus. In contrast to these findings the mean serum levels of IgG, IgA, and IgM in our group of keratoconus patients were not significantly different from the normal means as judged by a 1-sample Wilcoxon's test (Table 1).[12–14] Total serum immunoglobulin E, however, was found to be significantly increased in keratoconus when compared with our control population (p<0·0001) by Wilcoxon's rank sum test for 2 samples (Table 2); while the incidence of positive RAST tests in these patients, 59%, was significantly higher than in the controls, 13% (Table 3) (p<0·001 by the χ^2test. In particular reference to Table 3 it will be noted that a positive RAST result is arbitrarily taken as a combined RAST screen score of >2·1 (3×0·7). This incorporates samples with one single high value or several lower values. Also tabulated is the spectrum of specific immunoglobulin E response to specific allergens (Table 4).

Table 1 *Immunoglobulins G, A, and M in keratoconus*

Immunoglobulin (mg/dl)	*Control population*[13,14]	*Keratoconus* (n=27)	*Statistical significance*
IgG			
Mean	1200	1235	NS
Range	700-1900	653-1730	
IgA			
Mean	210	193	NS
Range	54-268	0-316	
IgM			
Mean	100	139	NS
Range	50-200	24-288	

SI conversion: g/l=mg/dl×0·01.
NS=not significant.

Table 2 *Total immunoglobulin E in keratoconus*

IgE (units/ml)	*Control population (n=46)*	*Keratoconus (n=27)*	*Statistical significance**
<120	43 (93%)	13 (48%)	
≥120	3 (7%)	14 (52%)	
Mean	35 U/ml	250 U/ml	$p<10^{-5}$
Range	<5–185	6·5–>1000	

*By Wilcoxon's rank sum test.

Table 3 *Specific immunoglobulin E in keratoconus (incidence of positive RAST screens)*

	Control (n=46)	*Keratoconus (n=27)*	*Statistical significance**
RAST score >2·1	6 (13%)	16 (59%)	p<0·0001

*By chi-square test.

We found no increased incidence of antinuclear antibodies, rheumatoid factor, antimitochondrial antibodies, or antibodies to smooth muscle in comparison with the controls.

Discussion

The main feature of this study is the measurement of serum levels of specific immunoglobulin E in addition to the measurement of total immunoglobulin E. In previous work only the total IgE has been estimated, and this has produced an overall incidence of 47% of keratoconus patients having a raised level of IgE; the

Table 4 *Positive RAST screens in keratoconus patients*

	IgE (units/ml)						
Patient no.	*Egg white*	*Milk*	*Fish (cod)*	*House dust mite*	*Cat epithelium*	*Dog dander*	*Poa pratensis*
1	0	0	0	16	13	2·4	0
2	0	0	0	17	0	0	0
3	0	0	0	>17·5	0	0	0
4	0	0	0	>17·5	0	0	1·9
5	0	0	0	0·8	6·4	1·4	>17·5
6	0	0	0	12	0	0·35	6·6
7	0	0	0	4·6	0	0	0
8	0	0	0	>17·5	0	3·8	2·1
9	0	0	0	15	1·35	0	16·5
10	0·4	0	0	7·6	0	0	0
11	0·8	0	0	>17·5	1·2	0	13
12	0	0	0·5	>17·5	0·5	0	2·8
13	0	0	0	>17·5	1·9	0	1·5
14	1·1	0	0	>17·5	0	0	0
15	0	0	0	>17·5	0	0	2·8

figure can be increased when a selected atopic group is studied and an incidence of 60% has been recorded. We can draw favourable comparisons in that our series, on unselected criteria, can be shown to have an incidence of 59% of keratoconus patients with abnormally raised serum levels of specific IgE.

It is of interest but of less than obvious clinical significance that the allergen of house dust mite has the highest incidence of specific IgE response in both the keratoconus and normal control groups. Moreover there is an example of a patient with keratoconus, raised total and specific IgE, and an unrecordable level of IgA. Transient IgA deficiency has previously been recorded in association with raised IgE.[10]

The pathological process remains obscure, but at the level of incidence postulated in this study it is important to consider why there should be recordable evidence of immunoglobulin-E-mediated hypersensitivity in keratoconus sufferers. The cornea is avascular and virtually acellular under normal circumstances. Any IgE-mediated response requires previous exposure of the immune system to a sensitising allergen. No definite histological evidence exists of corneal involvement in the immune response system. The timing of the exposure or some other extraneous factor may be of importance. A further examination of the patients, their immediate relatives, and possibly their environment may be beneficial in determining potential high-risk groups. A raised serum level of IgE may in itself be a high-risk factor.

Despite the interest of the above laboratory results it was not possible to confirm previous claims of further disturbance of immunopathology. No statistically significant change in other immunoglobulins was measured. Similarly no pattern of significance was detected in estimates of the levels of selected autoantibodies. Therefore no correlation can be postulated as in previous work, and we would be reluctant to accept a recent concept that keratoconus was a form of collagen disease expressed solely in ocular tissue. The pathology is perhaps misleading, because altered collagen appears to exist, but rather than presenting as a reaction to immunological assault it appears to be produced by abnormal keratocytes.[15 16] The reason for this apparent cellular disturbance is obscure, but in considering the activities of the cellular elements in the cornea we return to the original question of aetiology in keratoconus. No direct cause and effect has been established in this study, but we have categorically confirmed the high degree of association between keratoconus and raised immunoglobulin E.

The authors thank Dr E. M. Kirkwood and Dr E. P. Douglas for their help in preparation of the paper, and Dr I. C. McKay for his advice in statistical analysis.

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British Journal of Ophthalmology, 1982, **66**, 721–724

Effect on the intraocular pressure of hypotensive anaesthesia with intravenous trimetaphan

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SUMMARY The intraocular pressure was measured at 5-minute intervals with a Perkins applanation tonometer in 5 patients undergoing routine dacryocystorhinostomy under low-tension anaesthesia with a continuous intravenous infusion of trimetaphan (Arfonad), the systolic pressure being maintained at 60 mmHg. Twelve patients undergoing cataract surgery under the same premedication and anaesthesia but in whom the systemic blood pressure was maintained at normal levels served as controls. A sudden and dramatic lowering of the intraocular pressure to very low levels was noted when the systolic blood pressure was reduced to 60 mmHg. It seems likely that a collapse of the choroidal circulation rather than a decreased aqueous formation due to low perfusion pressure is the most likely cause of the sudden lowering of intraocular pressure.

Transient changes in intraocular pressure related to abrupt changes in systemic blood pressure possibly arising from changes in ocular blood volume have been described.[1] Variations in blood pressure produced alterations in the ocular blood flow, and Bill[2] and Cohan and Cohan[3] showed that the blood flow through the uveal tract varied directly with the level of systemic arterial pressure. Adler[4] showed that artifically induced changes in systemic blood pressure in animals were accompanied by parallel changes in the intraocular pressure, which were exaggerated if the cervical sympathetic trunk was divided. There is little doubt that ocular blood flow is influenced mainly by the systemic arterial pressure, lowering of which is bound to produce a fall in intraocular pressure.

Anaesthetic procedures are also known to cause alterations in intraocular pressure. Laryngoscopy and intubation caused a rise in intraocular pressure,[5] while intravenous induction agents caused a fall in intraocular pressure,[6] with the exception of ketamine, which had the opposite effect.[7] Intravenous suxamethonium caused a rise in intraocular pressure, while thiopentone sodium increased facility of outflow and so lowered the intraocular pressure.[8] Thus the intraocular pressure at the time of anaesthetic induction is subject to much variation.

Ganglion blocking agents like hexamethonium bromide (Vegolysen) given by intravenous infusion to lower systemic blood pressure to 90 mmHg were found to lower the raised intraocular pressure in patients with acute glaucoma to normal levels.[9 10] In hypertensive subjects pentolinium or hexamethonium bromide produced average falls of 9 mmHg in the intraocular pressure.[11] Niesel[12] found that hexamethonium given intravenously to rabbits always reduced the systemic blood pressure, intraocular pressure, and choroidal blood flow. Thus ganglion blocking agents which cause a fall in blood pressure also cause a fall in intraocular pressure, but with some drugs like intravenous tetraethyl ammonium bromide the fall in intraocular pressure was of a greater degree than could be explained by a mere fall in blood pressure,[13] and this suggests that, though the fall in intraocular pressure may be secondary to the systemic changes in the circulation, the ganglionic connections of the nervous pathways to the eye concerned with the regulation of aqueous formation or in the control of its outflow may also be involved.

The effect of hypotensive anaesthesia with hexamethonium in arresting bleeding into the anterior chamber associated with hyphaema has been observed.[10 14] Trimetaphan (Arfonad) is a short-acting ganglion blocking agent administered by continuous intravenous infusion. No studies have been reported on the effects of trimetaphan-induced low-tension anaesthesia on the intraocular pressure. It was therefore decided to study these effects in 5 patients undergoing routine dacryocystorhinostomy.

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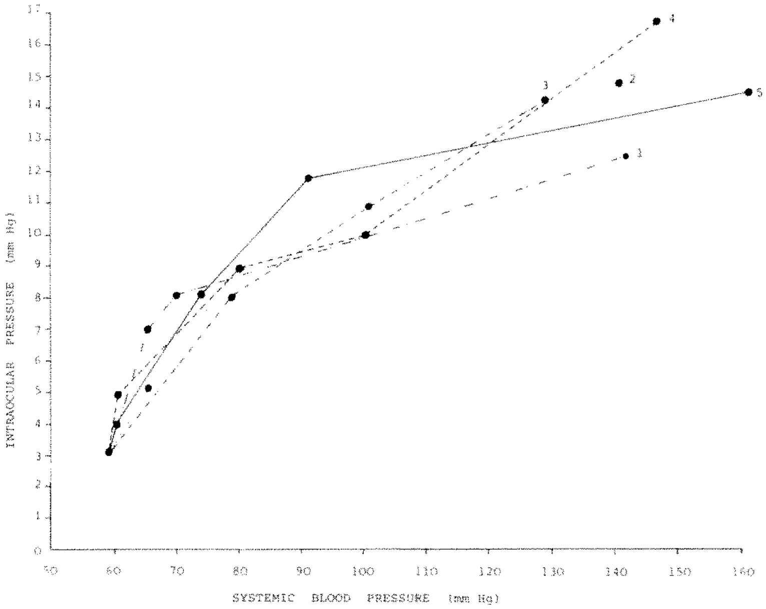

Fig. 1 *Variation of intraocular pressure with systemic blood pressure.*

Materials and methods

The intraocular pressure was measured at 5-minute intervals with a Perkins hand-held applanation tonometer[15] in 5 patients under low-tension anaesthesia in whom the systolic blood pressure was reduced to and maintained at 60 mmHg. Twelve patients undergoing cataract surgery under the same premedication and general anaesthetic but in whom the systemic blood pressure was maintained at normal levels served as controls. The intraocular pressure was measured in the unoperated eye.

Premedication in all patients was pethidine 50 mg and promethazine 25 mg given intramuscularly one hour before operation. General anaesthesia was induced with thiopentone sodium and suxamethonium, an endotracheal tube was passed, and the patient was maintained with nitrous oxide, oxygen, and halothane. Trimetaphan was infused intravenously in a continuous drip, the rate of the drip being controlled to maintain systolic blood pressure at 60 mmHg. The purpose of using this hypotensive agent was to secure a bloodless operation field. Brachial artery blood pressure and intraocular pressure were recorded the day before the operation, after administration of the premedication, and at 5-minute intervals after the administration of the general anaesthetic.

Results

In the 12 patients undergoing cataract surgery in whom the systemic blood pressure was maintained constant there was no significant change in the intraocular pressure. The maximal lowering of the intraocular pressure recorded in this group was a reduction of 3 mmHg occurring soon after induction of general anaesthesia and was probably due to the induction procedure.

In all 5 patients undergoing dacryocystorhinostomy a lowering of the systolic blood pressure to 60 mmHg produced a dramatic fall in the intraocular pressure to between 3–4 mmHg from the preoperative level of between 13–17 mmHg (Fig. 1). The intraocular pressure was observed to remain steady at this low level throughout the entire period during which the patient was under hypotensive anaesthesia. The maximal lowering of intraocular pressure was observed when the systolic blood pressure fell to 60 mmHg, and a rise of systolic blood pressure above 60 mmHg was associated with a corresponding rise in the intraocular pressure (Table 1). At no stage was the systolic blood pressure allowed to fall below 60 mmHG.

Discussion

Anatomically the eye has 2 separate systems of blood vessels—the retinal and uveal. The uveal vessels are peculiar in that they possess no precapillary sphincter, which is responsible for opening and closing the capillaries, with the result that the flow of blood in the uveal vessels is steady and not alternating[16] and there is a very high rate of blood flow through the uveal vessels.

In contrast to the kidney and brain, where owing to

Table 1 *Blood pressure and intraocular pressure recordings at 5-minute intervals in 5 patients undergoing hypotensive anaesthesia*

		Pre op.		*With hypotension*																
1.	BP (mmHg)	140	*	70	65	60	60	60	60	60	60	60		60	†	70		75	80	
	IOP	13		8	7	3	3	4	3	3	3	4		3		5		8	12	
2.	BP (mmHg)	140	*	90	80	80	65	60	60	62	60	60	†	70		80		85	90	
	IOP	15		12	9	9	5	3	3	3	3	3		7		7		8	8	
3.	BP (mmHg)	130	*	100	80	60	60	60	60	60	63	60	†	65		80		85		
	IOP	14		11	8	3	3	4	3	3	3	3		7		11		11		
4.	BP (mmHg)	145	*	100	80	60	60	60	62	60	60	65		60		60	†	70	80	90
	IOP	17		10	9	5	3	3	3	4	3	3		3		3		7	9	14
5.	BP (mmHg)	160	*	90	75	60	60	60	60	64	60	60		60	†	70		85	90	
	IOP	15		12	8	4	3	3	3	3	3	3		3		7		10	12	

Points at which the intravenous trimetaphan drip was started* and stopped†.

autoregulation a fall in perfusion pressure produces vasodilatation, thus maintaining a steady flow, there is no compensatory mechanism in the choroid, and the blood flow falls in proportion to the fall in perfusion pressure.[17] Though there is no reflex which significantly stabilises the intraocular pressure when the arterial blood pressure drops, a reflex mechanism does exist to protect the eye against a marked rise in pressure with systemic hypertension.[4]

A transverse section of the choroid shows it to be made up almost entirely of a series of blood vessels, and because of this 'erectile' potential of its vascular channels the choroid undoubtedly plays a role in the regulation of intraocular pressure. As the volume of the vascular bed of the choroidal circulation is several times that of the retinal circulation, the former makes a greater contribution to the maintenance of intraocular volume and intraocular pressure. Since it is mainly the degree of filling of the choriocapillaris and other blood vessels of the choroid which determines the volume of blood in the interior of the eye and hence the intraocular pressure, a systemic hypotension which reduces the blood flow in the choroid produces a sudden fall in intraocular pressure. This was clearly demonstrated in the rabbit, where the effect of carotid clamping was an immediate fall in intraocular pressure in the ipsilateral eye and a dramatic reduction in the blood flow through the choroid.[18] Stimulation of the peripheral end of the cut cervical sympathetic trunk caused a constriction of the uveal vessels, producing a reduced uveal blood flow and a marked fall in intraocular pressure. If the eyeball was enucleated or if the circulation of blood to the eye was interrupted, the intraocular pressure fell immediately. A rhythmic variation of the intraocular pressure occurring in phase with the cardiac cycle due to alterations in the volume of the vascular bed of the eye has also been demonstrated.[19] It is thus apparent that any factor which changes the filling of the choroidal reservoir must affect the intraocular pressure immediately.

The two fluids in the eye—blood and aqueous humour—contribute to the volume of the intraocular contents, and variations in the amount of either on account of a systemic hypotension will alter the intraocular pressure considerably. Formation of aqueous is partly due to secretion (75%) and partly due to ultrafiltration (25%). Ultrafiltration is the result of the hydrostatic pressure within the capillaries of the ciliary processes and is dependent on the ciliary artery blood pressure. If the systemic blood pressure falls, ultrafiltration is reduced as the blood supply to the ciliary body is reduced,[20] but secretion is not affected until the blood pressure falls to very low levels. It has been shown that the formation of aqueous persists in monkeys even at very low arterial pressure.[21] Hence, unless there is extreme systemic hypotension, formation of aqueous continues by the process of secretion.

It is known that the latent period associated with the rise in intraocular pressure which follows a rise in blood pressure is 0·1 s, and no mechanism other than the distension of the choriocapillaris could adapt so rapidly. It is unlikely that the rise in intraocular pressure is due to increased aqueous formation, in which case the latent period is bound to be longer. The rapid influx of blood into the choriocapillaris produced an immediated steep but transient elevation of intraocular pressure.[22] Our results show that a similar process could account for the fall in intraocular pressure which follows systemic hypotension, because a fall in intraocular pressure was observed with each stage of lowering of systemic blood pressure, the maximum fall in intraocular pressure occurring when the systolic blood pressure was reduced to 60 mmHg. Changes in intraocular pressure were almost exactly parallel to those in brachial artery blood pressure.

Thus it is more likely that the immediate and marked fall in intraocular pressure associated with systemic hypotension is due to a reduction in the volume of the vascular bed, and the persistence of the low intraocular pressure is due to the decreased formation of aqueous consequent upon the reduced flow of blood through the ciliary processes.

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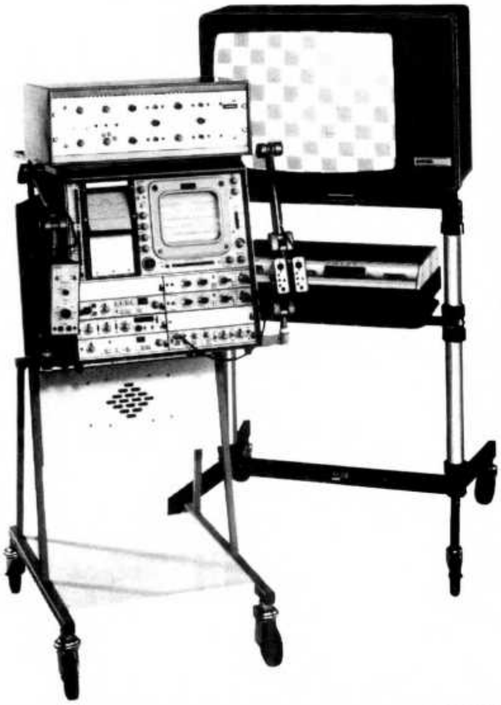

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British Journal of Ophthalmology, 1982, **66**, 725–727

Aneurysms in the ciliary body band confirmed by fluorescein gonioangiography

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SUMMARY Fluorescein gonioangiography was performed in a protracted case of Vogt-Koyanagi-Harada syndrome. Small, discrete, reddish lesions in the ciliary body band were confirmed to be aneurysms because they showed sharply defined hyperfluorescence shortly after fluorescein injection.

One of the authors (R.K.) has described, in patients with granulomatous uveitis,[1] whitish lesions in the ciliary body band which showed hyperfluorescence shortly after fluorescein injection. The hyperfluorescent dots were considered to be granulomas in the ciliary body band. The purpose of this communication is to describe small, discrete, reddish lesions which have shown sharply defined hyperfluorescence shortly after fluorescein injection in a protracted case of Vogt-Koyanagi-Harada syndrome.

Case report

Complaining of blurred vision in both eyes, a 27-year-old man was seen by an ophthalmologist 6 years earlier. With the diagnosis of Vogt-Koyanagi-Harada syndrome systemic corticosteroids were instituted. A week later he was referred to our clinic. When he was seen in our clinic, vision was 20/40 with myopic correction of −6·5 D in both eyes. Applanation pressure was 15 in the right and 13 mmHg in the left eye. The cornea was clear except for some keratic precipitates in both eyes. The anterior chamber was deep in both eyes. Biomicroscopy revealed flare and cells in both anterior chambers. Ophthalmoscopy revealed multiple serous retinal detachments in both eyes. Results of laboratory examinations, including complete blood cell count, electrolytes, cholesterol, glucose, and liver and renal functions, were normal. A serological syphilitic test, the rheumatoid arthritis titre, and C-reactive protein value were negative. An antistreptolysin 0 value of 50 Todd units was also obtained. Although he had complained of buzzing in the ears, otological examinations revealed no abnormal findings. The diagnosis of Vogt-Koyanagi-Harada syndrome was made. Systemic corticosteroids were given over the following 2 months, resulting in subsidence of the disease.

Since then the patient was seen on follow-up examinations by an ophthalmologist to have suffered several attacks of mild iritis. He was referred to our clinic again on 26 May 1981 because of increased intraocular pressure in the left eye. On examination vision was 20/25 with myopic correction of −9 D in the right and 20/40 with myopic correction of −8 D in the left eye. Applanation pressure was 12 in the right and 55 mmHg in the left eye. The anterior chamber was deep in both eyes. The cornea was clear in the right and slightly oedematous in the left eye. Biomicroscopy after peroral 50% glycerol (2 ml/kg) revealed clear aqueous humour in both eyes. The lens in both eyes showed slight posterior subcapsular opacities, probably due to prolonged use of corticosteroids. Ophthalmoscopy revealed in both eyes a diffusely red fundus associated with numerous depigmented foci. Fluorescein angiography of the fundus showed no newly formed retinal or choroidal vessels nor leakage of dye. Gonioscopy revealed a wide open angle with wide ciliary body band in both eyes. However, newly formed angle vessels were seen in both eyes extending from the angle recess toward the trabecular meshwork, associated with small discrete reddish lesions in the ciliary body band. The left eye was affected the more severely. Fluorescein gonioangiography showed clearly the newly formed angle vessels shortly after fluorescein injection in both eyes (Figs. 1 and 2). The reddish lesions in the ciliary body band also showed a sharply defined hyperfluorescence shortly after fluorescein injection in both eyes (Figs. 1 and 2). Both

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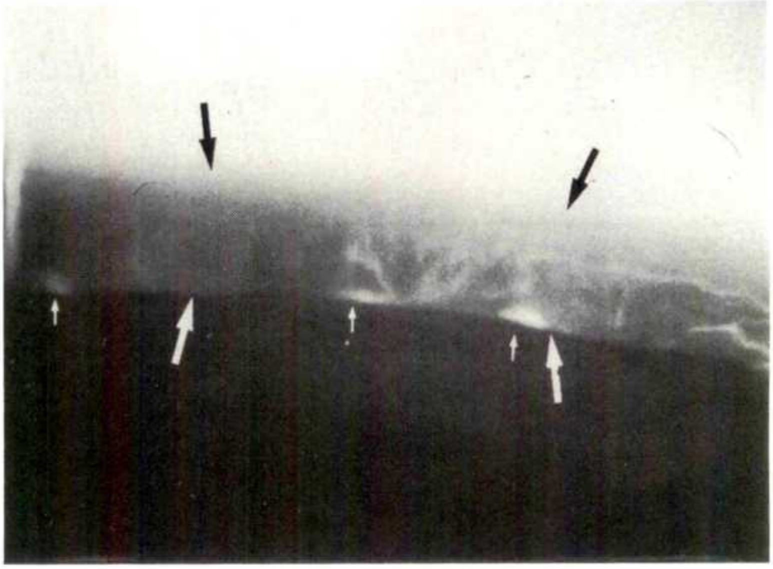

Fig. 1 *Fluorescein gonioangiogram in the lower nasal quadrant of the right eye 15 seconds after fluorescein injection, showing hyperfluorescent dots (small white arrows) corresponding to the reddish lesions associated with newly formed vessels. Large white arrows indicate the iris root, and black arrows indicate Schwalbe's line.*

visual fields were normal. Oral acetazolamide 250 mg once in the morning was instituted, resulting in return to normal of the intraocular pressure in the left eye. Since then examinations of the patient at intervals of a month have revealed no changes in either eye.

Discussion

In previous papers[1 2] one of the authors (R.K.) presented several characteristic findings obtained by the original method of fluorescein gonioangiography[2] as follows: (i) no staining or leakage in normal persons; (ii) increased visibility of newly formed angle vessels; (iii) leakage from the recessed angle in cases with traumatic angle recession; (iv) vigorous leakage from the angle recess in a case with Behçet's disease during an attack of uveitis; (v) hyperfluorescent dots in the ciliary body band corresponding to the whitish lesions in cases with granulomatous uveitis. Thus fluorescein gonioangiography as well as fundus angiography offers useful informations in the diagnosis of eye disorders. In the present study we have dealt with reddish lesions

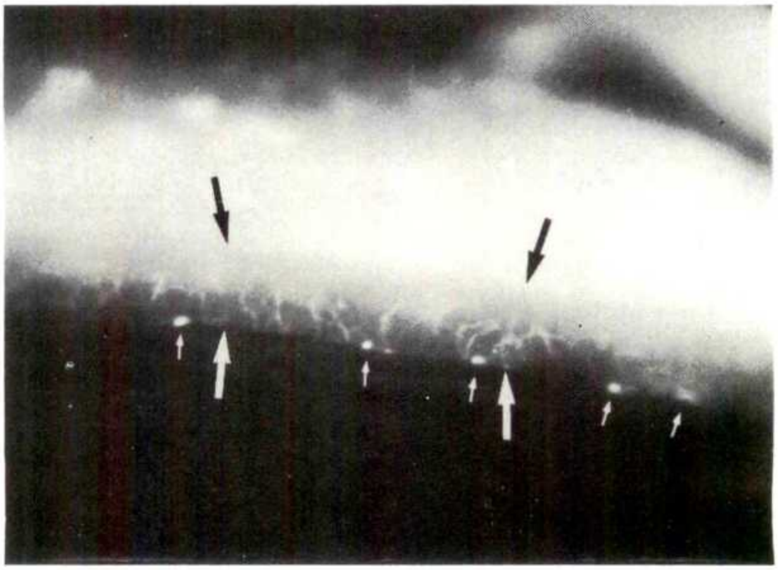

Fig. 2 *Fluorescein gonioangiogram in the lower temporal quadrant of the left eye 15 seconds after fluorescein injection, showing hyperfluorescent dots (small white arrows) corresponding to the reddish lesions associated with newly formed vessels. Large white arrows indicate the iris root, and black arrows indicate Schwalbe's line.*

in the ciliary body band. There are several reports of haemorrhages in the angle.[3 4] For example, Moreu (cited by Troncoso[3]) described cases of syphilitic iritis with intense congestion of the root of the iris, ciliary body oedema, and small haemorrhages. To the best of our knowledge, however, there are no reports of aneurysms in the angle. Their absence may be attributed to a lack of gonioangiographic studies, because it is well known that only fluorescein angiography can differentiate aneurysms from haemorrhages clinically. In the present study aneurysms in the ciliary body band associated with newly formed vessels were demonstrated by means of fluorescein gonioangiography.

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British Journal of Ophthalmology, 1982, **66**, 728–731

Ophthalmia neonatorum in the 1980s: incidence, aetiology and treatment

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SUMMARY In a survey of 450 consecutive births in Southampton a 12% incidence has been found of ophthalmia neonatorum. Bacterial pathogens were isolated from only one-third of the cases, while nonpathogens were isolated from as many cases as controls. There was an incidence of chlamydial infection of 3·7 per 1000 live births, while *Neisseria gonorrhoeae* could not be found. Chloramphenicol is recommended for topical antibacterial treatment, but chlamydial infection will not respond; it must be considered in 'resistant' cases, when both the neonate and the parents will need treatment with erythromycin or tetracycline.

Conjunctivitis is frequently seen in newborn babies, yet its aetiology often remains obscure. In Britain *Staphylococcus aureus, Streptococcus pneumoniae* and *Haemophilus* sp. are established pathogens, as was *Neisseria gonorrhoeae*. However, *Pseudomonas aeruginosa,*[1] *Klebsiella* spp., *Escherichia coli, Str. viridans* and *Staph. albus,*[2] *herpes simplex* virus types I and II,[3] adenovirus type 8[4] and *Mycoplasma* spp.[5 6] have also been isolated from cases of ophthalmia neonatorum (ON). *Chlamydia trachomatis* is also being recognised as of increasing importance as a cause of ON.[7] Chlamydial ON differs from other infections by being contracted in the intrapartum period but developing after the baby has left hospital. It does not respond to the usually applied topical antibiotics and is known to progress to further ocular and extraocular complications.[8–11]

This study set out to establish prospectively the incidence and type of ON in Southampton, including its natural history and most appropriate treatment. Currently used antibiotic therapy was determined by a survey of general practitioners (GPs), to whom many cases present because of our existing policy of early discharge of the mother from hospital.

Materials and methods

The study population consisted of consecutive births in the Maternity Unit of Southampton General Hospital between 1 January and 31 March 1981. All mothers were resident in the Southampton area. Each infant was observed for a period of 2 weeks for the development of ON. This was diagnosed by the presence of an acute, overt ocular discharge and conjunctival hyperaemia. Neonates were excluded if the discharge did not resolve but became continuous owing to anatomical abnormalities such as nasolacrimal duct obstruction. The observation was continued outside the hospital by the GP, and each case was visited by one of us (J.M.P.).

Cultures were collected from the inferior palpebral conjunctival surface on 2 sterile cotton-wool swabs. One swab was placed in sucrose phosphate transport medium and the material inoculated within one hour on to diethylaminoethyl (DEAE)-dextran-treated HeLa 229 cells for the isolation of *C. trachomatis* by the method previously described.[12] Material from the second swab was immediately cultured on to chocolate agar for bacteria at 37°C in 5% CO_2 in air for 48 hours, before being transferred to blood agar to observe for haemolysis by streptococci. Bacteria were identified with standard laboratory techniques. Antibiotic sensitivity testing was performed by the disc method.[13] Anaerobic cultures were not carried out, as the number of samples which could be taken was limited by the quantity of the discharge; moreover anaerobes are considered a rare cause of ON.[5] Control cultures were collected from neonates with normal eyes individually matched for age at onset of symptoms, type

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of delivery, location of delivery, and location of rooming-in (post-natal ward).

One hundred and five general practitioners in Southampton were surveyed for their management of ON and asked to list their antibiotic regimen for arbitrary therapy. General practice was considered the most likely discipline to which cases of chlamydial ON would initially present.

Results

In the period of the study there were 450 deliveries; 54 of the babies developed ON, giving a 12% incidence in unselected births. The organisms isolated from 42 of these cases in which swabs were collected are given in Table 1 and are grouped into recognised pathogens and nonpathogens. The results from the matched control neonates are also included. By the χ^2 test *Staphylococcus aureus* was not found significantly more often among cases than controls ($p > 0 \cdot 10$) but *Streptococcus viridans* was ($p < 0 \cdot 001$). *N. gonorrhoeae* was never isolated despite the use of a sensitive culture technique for it. Recognised pathogens were found more often among cases than controls ($p < 0 \cdot 001$). There was no significant difference between the numbers of nonpathogens in cases and controls, but there was a higher rate of sterile cultures from the control population. *C. trachomatis* was isolated on only one occasion (listed in Table 1). It was decided therefore to extend the study to another 100 neonates to look only for this organism; one further neonate was identified with it—inclusion conjunctivitis of the newborn (ICN).

Antibiotic sensitivity tests showed that chlortetracycline was effective against all the bacteria associated with ON and chlamydia of ICN. Chloramphenicol was similarly found to be effective against all the bacterial cases but not against *C. trachomatis*. Streptococci were resistant to gentamicin and framycetin (neomycin). Sulphonamide was not generally effective.

Seventy-nine (75%) of general practitioners answered the questionnaire about prescribing habits for ON. Of these, 59 (75%) prescribed various antibiotics (Table 2), while 15 (19%) only occasionally did so. Chloramphenicol was the most popular and used by 66% of the GPs, while chlortetracycline was used by only 4%. Many replies indicated that failure to respond to topical antimicrobial therapy combined with washing the affected eye rarely occurred. The number of topical antibiotic applications and the duration of therapy was found to be very varied; the commonest regimen was 4-hourly. Although chlamydial infection of the cervix is sexually transmissible, only 18% of the GPs would have referred or treated both parents, so as to eradicate carriage of *C. trachomatis* and prevent future offspring from developing ICN.

Table 1 *Organisms isolated from 42 cases and matched controls*

Bacteria	*Ophthalmia neonatorum*	*Control neonates*
PATHOGENS		
Staph. aureus	2	2
Staph. aureus and Chlamydia trachomatis	1	0
Staph. aureus and Streptococcus viridans	1	0
Str. viridans	6	2
Str. milleri	1	0
H. influenzae	2	0
Haemophilus sp.	1	0
Escherichia coli	1	0
Subtotal	15	4
NONPATHOGENS		
Mixed *Staph. epidermidis*, diphtheroids, and micrococci	11	16
Pure micrococci	2	4
Pure diphtheroids	1	0
Subtotal	14	20
No growth	13	18
Total	42	42

Table 2 *Types of antibiotics prescribed by 59 general practitioners*

Type of antibiotic	*% of GPs prescribing each antibiotic*
Chloramphenicol	66
Sulphacetamide	12
Gentamicin	9
Neomycin	6
Chlortetracycline	4
Framycetin	2
Polymyxin + bacitracin	1

Discussion

From 450 unselected deliveries in Southampton 12% of infants developed ON. In 1977 among newborn babies in Harrow the incidence was a comparable 8·4%,[5] showing that in both areas ON is a common condition. However, in America, where Credé's prophylaxis is routinely used, Armstrong *et al.*[14] found the incidence to be 1·6%, but this has to be contrasted with toxic effects that can occur with it.

The unpaired Student's *t* test was used to compare those neonates who subsequently developed ON with a random control population born in the same maternity unit and over the same period. It was found that health in the immediate postpartum period, as judged by the Apgar score at one minute, did not affect the chance of developing ON: neither did the length of the second stage of labour, nor mechanical intervention at birth. But the neonate's conjunctiva is prone to infection, not only because there are low levels of antibacterial tear proteins, namely, lysozyme[15] and IgA, but also because the tear flow and film are only beginning to develop.

Staphylococcus aureus was not found more often among cases than among controls. This is probably because there was no obvious cross-infection within the unit and no outbreaks occurred due to it. Other workers have found it to be important.[14 16] *Streptococcus viridans* was isolated significantly more often from cases (17% of the total) than controls. Previous studies by Prentice *et al.*[5] and McGill[2] have shown *Str. viridans* to be isolated in 16% and 18% of cases of ON respectively and in the latter showed a positive correlation with the presence of pus cells. 'Nonpathogenic' skin flora was found alike in ON and controls and can probably be ignored as a cause of ON.

There were two cases of *C. trachomatis* ICN among 550 consecutive deliveries, giving an incidence of 3·7 per 1000 live births. This compares with American studies which put the incidence between 1·4 and 4·4 per 1000 live births.[14 17–19] However, British studies have found *C. trachomatis* to be less prevalent than in Southampton. Prentice in Harrow in 1977[5] did not find any cases of ICN among 103 cases of ON, whereas McGill[2] in Ayrshire found 2 cases of ICN among 213 cases. However, in a selected study of severe purulent ocular discharge in neonates in eastern Glasgow in 1979 38% of 199 specimens were found to grow *C. trachomatis*.[20] In Liverpool[21] *C. trachomatis* was recovered from 36% of 81 cases of ON preselected for their resistance to conventional treatment.

Our failure to isolate organisms from 30% of cases of ON could be partly explained by the fact that we did not culture for *Mycoplasma*, for which an infection rate of 3% has been found,[6] or viruses. A more likely explanation is that initial inadequate tear flow rather than an infectious aetiology is involved. Support for this latter hypothesis is presented by a number of observations. Firstly, the natural history is for a tendency towards spontaneous resolution within 48 to 72 hours even in those cases with a frank purulent discharge, provided the affected eyes are washed with sterile saline. Secondly, in our survey 19% of GPs prescribed antibiotics only occasionally yet at the same time claimed as much success in treating the condition as those who prescribed antibiotics in all cases. Thirdly, 12% of GPs prescribed sulphacetamide, yet it was found that organisms from cases of ON are not generally sensitive to it.

Chlortetracycline is the only effective antibiotic against most bacteria of ON and chlamydia of ICN. However, its indiscriminate use would lead to masking of those neonates with ICN and hence the failure to identify asymptomatic parenteral carriage. Neomycin and chloramphenicol are both active against most of the bacteria causing ON, with chloramphenicol being effective against streptococci. Neomycin has the advantage that it does not mask chlamydial ICN[22] but also has the serious disadvantage of being ineffective against streptococci and is associated with contact sensitisation.

The rarity with which *C. trachomatis* is isolated (in Southampton 3% of all cases of ON) and the laborious and costly isolation procedure for it suggest that there should be a high index of clinical suspicion, such as severe chloramphenicol-resistant conjunctivitis, before conjunctival swabs are collected for chlamydial culture in those areas fortunate enough to have a chlamydial culture service. Ideally, to increase the likelihood of *C. trachomatis* isolation, swabs should be collected into special transport medium[12] after 2 days' treatment with neomycin.[22] The treatment of choice for ICN is topical chlortetracycline for several days and oral erythromycin 30 mg/kg/day for 3 weeks.[23] Oral chemotherapy is also necessary to reduce pharyngeal carriage.[24] Both parents of neonates with proved ICN must also receive effective antichlamydial therapy—250 mg oral tetracycline or erythromycin 4 times a day for 3 weeks, with erythromycin being the drug of choice if breast feeding.

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British Journal of Ophthalmology, 1982, **66**, 732–735

Immunoassay of tear lysozyme in conjunctival diseases

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SUMMARY The tear lysozyme content in 111 normal subjects and in 159 patients with various conjunctival diseases was determined by a single radial immunodiffusion technique. Tear lysozyme level in normal people was 1·33 mg/ml. (SI conversion: mg/ml=g/l.) The mean tear lysozyme levels in patients with chronic irritative conjunctivitis (0·97 mg/ml) and nutritional deficiency with epithelial xerosis (0·76 mg/ml) were significantly lower than in the normal controls. The mean tear lysozyme levels in tears from patients with vernal conjunctivitis (1·20 mg/ml), phlyctenular conjunctivitis (1·10 mg/ml), and acute bacterial conjunctivitis (1·48 mg/ml) were not significantly different from those in the normal controls. Superimposition of acute bacterial conjunctivitis on trachoma did not alter the low tear lysozyme level that existed before in these patients.

Lysozyme (muramidase) is present in high concentration in normal human tears. Its role is uncertain. In view of the bacteriolytic property of lysozyme[1,2] it has generally been held that the enzyme in tears acts as a protective agent against bacterial infection.

Although there are several studies on the tear lysozyme level in keratoconjunctivitis sicca,[3-10] only a few are available on it in other conjunctival diseases.[11-13] The tear lysozyme level in patients with trachoma is low.[14] The purpose of the present study was 2-fold: (1) To investigate whether there is any alteration in the tear lysozyme level in patients with other conjunctival diseases, and (2) To investigate whether superimposition of acute bacterial conjunctivitis in patients with trachoma alters the existing low tear lysozyme level.

Subjects and methods

The study was carried out among 159 patients with various conjunctival diseases and 111 healthy people chosen consecutively from the Outpatient Department of Guru Nanak Eye Centre, New Delhi. The latter group served as control for all the disease groups and comprised people who had no ocular or systemic disease and had attended the hospital only for a routine check-up.

An earlier report by the present authors has already described the lysozyme level among normal Indian people by the immunoassay method.[14] However, for the purpose of the present investigation it was considered advisable to examine a fresh group of normal people to serve as concurrent control. The diagnosis of conjunctival diseases was based on detailed clinical examination, including slit-lamp biomicroscopy, ophthalmoscopy, and relevant bacteriological and other laboratory investigations. The patients with chronic irritative conjunctivitis were factory workers whose eyes were exposed to noxious fumes for many months. Their chief complaints were watering, burning, stinging, foreign body sensation, and an urge to

Table 1 *Pathogenic organisms identified on culture in cases of acute bacterial conjunctivitis*

Pathogenic organisms identified	*Acute bacterial conjunctivitis* (28 cases)*	*Trachoma with acute bacterial conjunctivitis† (20 cases)*
Staphylococcus aureus	14	13
Pneumococcus	8	5
Pseudomonas pyocyanea	6	3
Streptococcus viridans	5	3
Streptococcus pyogenes	4	4
Proteus vulgaris	3	2
Klebsiella pneumoniae	2	0
Escherichia coli	1	3
Alpha-haemolytic streptococci	2	1

*More than one organism was isolated in 18 patients.
†More than one organism was isolated in 12 patients.

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Table 2 *Age and sex distribution of healthy subjects and patients with conjunctival diseases*

Sex	*Normal*	*Epithelial xerosis*	*Vernal conjunctivitis*	*Phlyctenular conjunctivitis*	*Acute bacterial conjunctivitis*	*Chronic conjunctivitis*	*Trachoma*	*Trachoma acute bacterial conjunctivitis*
Male	55	15	10	13	17	13	16	11
Female	56	10	7	5	11	7	15	9
Total	111	25	17	18	28	20	31	20
Age (yr)								
≤15	20	16	5	14	3	0	2	2
16–30	37	9	12	4	13	9	10	8
31–45	26	0	0	0	11	11	16	8
≥46	28	0	0	0	1	0	3	2
Total	111	25	17	18	28	20	31	20

rub their eyes. Hyperaemia of the conjunctiva was a prominent clinical feature and was particularly marked in the area of the palpebral aperture. On slit-lamp examination there were no follicles, scarring of the conjunctiva, or associated corneal lesions. The pathogens identified on conjunctival smears and cultures in cases of acute bacterial conjunctivitis are given in Table 1. The bacterial infection was mixed in majority of the patients.

A general physical examination was made in every patient, and those who had no ocular or systemic affliction other than the conjunctival disease were chosen. None of the patients received any medication before or at the time of the study.

Stimulated tear samples of 100 to 200 μl were collected by a method described previously[15] and stored at −20°C until assayed. Lysozyme was quantified by a single radial immunodiffusion technique originally described by Mancini *et al.*[16] after diluting the tear samples 1:25 with phosphate buffered saline (pH 7·4). The technique has been described in detail.[14] Monospecific rabbit antihuman lysozyme serum and the reference standard were obtained from Behring Institute, West Germany. A standard curve was constructed for each plate and the concentration of lysozyme in tear samples was determined with reference to the standard curve.

Results

The age and sex distribution of normal people and the patients are given in Table 2. Tear lysozyme was found in all the samples in measurable quantity. In normal people the overall mean value of tear lysozyme was 1·33±0·69 mg/ml. (SI conversion: mg/ml=g/l.) There was no significant difference ($t=1{\cdot}07$, DF 109, $p>0{\cdot}30$) between the levels in males (1·41±0·70 mg/ml) and that in females (1·27±0·67 mg/ml). The tear lysozyme levels in the different age groups are shown in Table 3. It can be seen that the lysozyme level was low in the young, rose with age, and started falling after the age of 30 years. Since the tear lysozyme level in normal people varied with age, it was necessary for comparison to take separate controls matched for age from among the normal people for each disease group.

The mean levels of tear lysozyme in controls matched for age and in the disease groups are given in Table 4. The mean tear lysozyme was significantly decreased in the cases of nutritional deficiency with epithelial xerosis ($p<0{\cdot}01$) and in chronic irritative conjunctivitis ($p<0{\cdot}001$) as compared with normal healthy people of the respective age groups. It was not significantly altered in vernal conjunctivitis, phlyctenular conjunctivitis, and acute bacterial conjunctivitis. The mean tear lysozyme in patients with trachoma with superimposed acute bacterial conjunctivitis was compared with that in patients with trachoma after matching for age, and the difference failed to attain statistical significance ($p>0{\cdot}05$).

Discussion

The techniques employed for the estimation of tear lysozyme were difficult for routine application and for comparison, and the values obtained varied widely.[4 5 17 18] Bonavida and Sapse[19] introduced a method based on the bacteriolytic action of lysozyme on the cell wall of *Micrococcus lysodeikticus*. Johansson and Malmquist[20] observed that the bacteriolytic

Table 3 *Distribution of tear lysozyme level in the various age groups in normal subjects*

Age (years)	*No. of subjects*	*Mean±SD (mg/ml)*	*Coefficient of variation (%)*
≤15	20	0·83±0·34	41·0
16–30	37	1·64±0·73	44·5
31–45	26	1·45±0·62	42·8
≥46	28	1·24±0·63	50·8

SI conversion: mg/ml=g/l.

Table 4 *Tear lysozyme levels in controls matched for age and those in patients with conjunctival diseases*

Disease groups	*Number of patients and normal controls*	*Lysozyme in mg/ml*					
		Disease groups		*Normal controls matched for age*			
		Mean±SD (SE)	*CV%*	*Mean±SD (SE)*	*CV%*	*t*	*p*
Epithelial xerosis	25	0·76±0·44 (0·09)	57·9	1·20±0·64 (0·13)	53·3	2·87	<0·01
Vernal conjunctivitis	17	1·20±0·60 (0·15)	50·0	1·18±0·66 (0·16)	55·9	0·09	>0·90
Phlyctenular conjunctivitis	18	1·10±0·69 (0·16)	62·7	0·98±0·51 (0·12)	52·0	0·61	>0·50
Acute bacterial conjunctivitis	28	1·48±0·66 (0·12)	44·6	1·47±0·59 (0·11)	40·1	0·09	>0·90
Chronic irritative conjunctivitis	20	0·97±0·46 (0·10)	47·4	1·81±0·81 (0·18)	44·8	4·03	<0·001
Trachoma	31	0·89±0·36 (0·07)	40·4	1·52±0·75 (0·13)	49·3	4·19	<0·01
				Trachoma patients matched for age as control			
Trachoma with acute bacterial conjunctivitis	20	1·06±0·47 (0·10)	44·3	0·83±0·38 (0·09)	45·8	1·70	>0·05

CV = coefficient of variation.
SI conversion: mg/ml = g/l.

lysozyme determination is not a specific enzyme assay and is probably influenced to some extent by factors other than the lysozyme activity. To avoid such influences tear lysozyme levels were measured by a single radial immunodiffusion method.

Anderson[13] studied cases of epithelial xerosis and found the tear lysozyme to be much lower. Present findings are in agreement with his observations. Thompson and Gallardo[12] and Harada and associates[21] have shown that the chief sources of lysozyme in tears is the lacrimal gland rather than the mucous gland of the conjunctiva. It is therefore assumed that the cases of nutritional deficiency with epithelial xerosis have a decreased production of the enzyme by the lacrimal gland.

Ridley[1] reported a low level of lysozyme in tears in phlyctenular conjunctivitis and considered it to be due to associated excessive tearing. However, recent studies have shown that there is no correlation between the titre of lysozyme in the tear fluid and the rate of tear flow.[8,9,11,22] We did not find the tear lysozyme level in this disease to be significantly different from that of healthy subjects.

Erickson and associates[18] reported the tear lysozyme level to be low in eyes exposed to industrial fumes. The present findings are similar. This low level may be due to destruction of lysozyme in the conjunctival sac or to binding of the lysozyme locally to the tissue by noxious agents.[11]

Reports on the tear lysozyme level in patients with acute bacterial conjunctivitis are contradictory.[4,12,23,24] Some authors have reported a low level of tear lysozyme in these patients and attributed this to excessive tearing associated with the disease.[4,23] It has already been pointed out that excessive tearing does not alter the lysozyme level in tears.[8,9,11,22] Janke and associates[24] on the other hand observed that the lysozyme level was probably slightly higher in acute bacterial conjunctivitis. Gordon and associates[25] and McClelland and van Furth[26] have demonstrated that the neutrophils contain lysozyme which is liberated from them during degeneration and cell death. Therefore the lysozyme content of tears from patients with acute bacterial conjunctivitis may be expected to be high. However, no significant alteration was found in the tear lysozyme level in such patients as compared with controls. This indicates that the neutrophils present in tears of such patients are not numerous enough to contribute significantly to the lysozyme content of tears.

The tear lysozyme levels in patients with trachoma have been reported to be low.[14] This low lysozyme level in patients with trachoma probably makes them more vulnerable to secondary bacterial infections, which are frequently associated with trachoma. Ridley[27] had stated that while the normal lysozyme content of tears might be effective against some pathogenic bacteria, the lysozyme level needed to be decreased only very slightly to be totally ineffective against all pathogens. A group of patients with trachoma were examined as concurrent controls for the group of patients with trachoma superimposed with acute bacterial conjunctivitis. There was no significant difference in the tear lysozyme levels between the 2 groups. This again suggests that acute bacterial conjunctivitis does not alter the lysozyme level in tears significantly.

We thank Mr G. P. Mathur, statistician, New Delhi Tuberculosis Centre, New Delhi, for the statistical analysis of the data.

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British Journal of Ophthalmology, 1982, **66**, 736–741

Ocular pathology of the Majewski syndrome

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SUMMARY A case report with ocular histopathological findings of the Majewski form of short rib polydactyly is presented. The findings included cataract and optic atrophy. The systemic features of this syndrome and the ophthalmic findings are discussed in relation to the Meckel syndrome and trisomy 13, from which it must be differentiated.

The association of lethal neonatal dwarfism, narrow thorax, and polydactyly is well established in the older literature particularly from the syndromes described by Jeune and Ellis-Van Creveld.[1-4] There has been renewed interest in this subject and the classification of short rib polydactyly since Majewski *et al.* described the features of a lethal congenital syndrome characterised by short ribs and limbs, polysyndactyly, median cleft lip, and anomalies of the epiglottis, visceral organs and genitalia.[5] Subsequent recognition of clinical and radiological differences became apparent as additional cases were studied and gave rise to the reclassification of short rib polydactyly (SRP) to include type I of Majewski and type II of Saldino-Noonan.[6] Additional reports have demonstrated other variants of this condition, several of which may also be distinct forms.[7-16]

Necropsy reports have been conspicuous for the absence of information on the ophthalmic findings in these cases. We present here the ocular histopathological findings in the Majewski type of SRP and discuss the differential diagnosis and clinicopathological features of this disease group. Heightened awareness of neonatal dwarfism syndromes may lead to the gathering of more information on the ophthalmic aspects of SRP.

Case report

A 3250 g male was the product of a full-term gestation. The family history was negative for known congenital abnormalities. Parental consanguinity was denied. The mother was gravida 2, para 1, and apart from a first trimester respiratory infection had had a normal pregnancy. She had taken no medication except for an occasional aspirin. There was a normal, spontaneous vaginal delivery. The Apgar score was 7 at one minute and 8 at 5 minutes. Multiple congenital abnormalities and mild respiratory distress were noted, and the baby was placed in special care facilities.

At birth the baby's weight, length, and head circumference were all in the 50th percentile. There was a midline partial cleft lip with a highly arched but intact palate. The chest circumference was small (28 cm) and the extremities were short, particularly in their lower third. The interphalangeal creases of each fifth finger were almost superimposed. Bilateral preaxial hexadactyly of the feet was present with syndactylous duplication of the big toes. Direct ophthalmoscopic examination of the fundi did not reveal abnormalities. Physical examination of the heart, abdomen, genitalia, and neurological system was normal. The karyotype was 46 XY and showed normal Giemsa banding.

Oxygen therapy stabilised the respiratory distress to the extent that room air was tolerated with tachypnoea (80-100/minute). Tube feedings were required. Laboratory tests including complete blood count, urine analysis, blood cultures, blood urea nitrogen (BUN), and electrolytes were normal. Bilirubin was 1·3 mg/dl direct and 3·0 total (22 and 51 μmol/l).

Radiological examination at 2 days of age revealed very short ribs involving all 12 pairs with a resultant narrow thorax. In the lower part the lateral rib cage was concave rather than convex. Sternal maturation was advanced, the skull was normal, and the mandible was V-shaped. Other major skeletal

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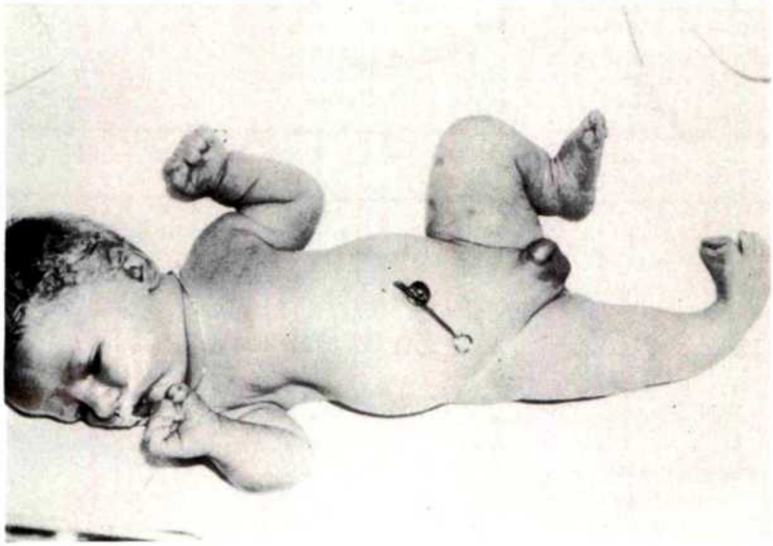

Fig. 1 *Neonate with short rib polydactyly syndrome.*

anomalies included excessively short tibias with medial bowing and preaxial hexadactyly of both feet (Fig. 1).

The child was discharged from the hospital after 17 days. There was failure to thrive despite continued tube feeding and death ensued at 8 weeks of age.

NECROPSY FINDINGS

The multiple congenital abnormalities as described above were confirmed. Alveolar haemorrhages in the lungs and right cardiac ventricular dilatation were present. There were no additional congenital abnormalities of the internal organs. Histopathological study of the brain revealed anoxic and metabolic encephalopathy, acute and chronic, and very minor cerebellar dysgenesis. Additional details of the clinical history, radiographic findings, and necropsy may be found in the initial report on this patient by Bidot-Lopez *et al.*[11]

Gross and microscopic findings for the right and left eyes were essentially the same.

Gross examination of right eye. The right globe measured 19×20×16 mm with 5 mm of optic nerve attached. The pupil measured 3 mm. The sclera had a bluish hue and the globe transilluminated well. The cornea was somewhat distorted. The globe was sectioned in the horizontal plane. The anterior chamber and angle, iris, and ciliary body appeared to be within normal limits. The lens appeared yellow. The vitreous was slightly cloudy. The retina, choroid, disc, and macula all appeared within normal limits.

Microscopic findings. The corneal epithelium was within normal limits. The stroma was slightly thickened and hypercellular but within normal limits for age. Descemet's membrane and the endothelium were within normal limits. The anterior chamber was formed and the angle structures were well differentiated. There was vacuolation of the iris (Fig. 2) pigment epithelium and increased cellularity of the stroma, normal for that age. The ciliary body was unremarkable. The lens revealed early nuclear sclerosis, and there was posterior displacement of the epithelial bow. There was bladder cell degeneration of the lens cortex. Remains of the vitreous were adherent to the peripheral retina and ciliary body.

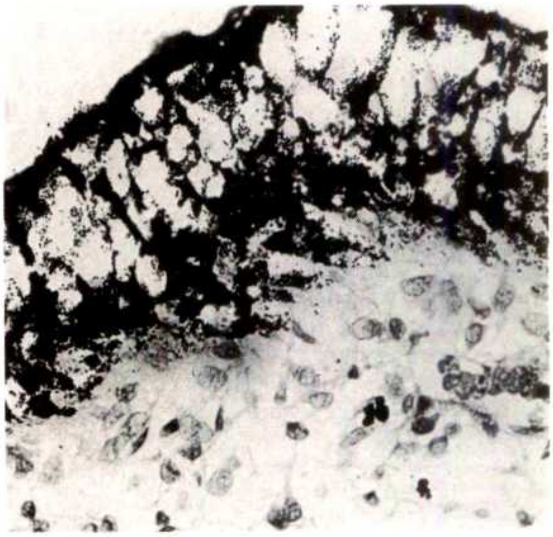

Fig. 2 *Vacuolisation of iris pigment epithelium. (Haematoxylin and eosin, ×300).*

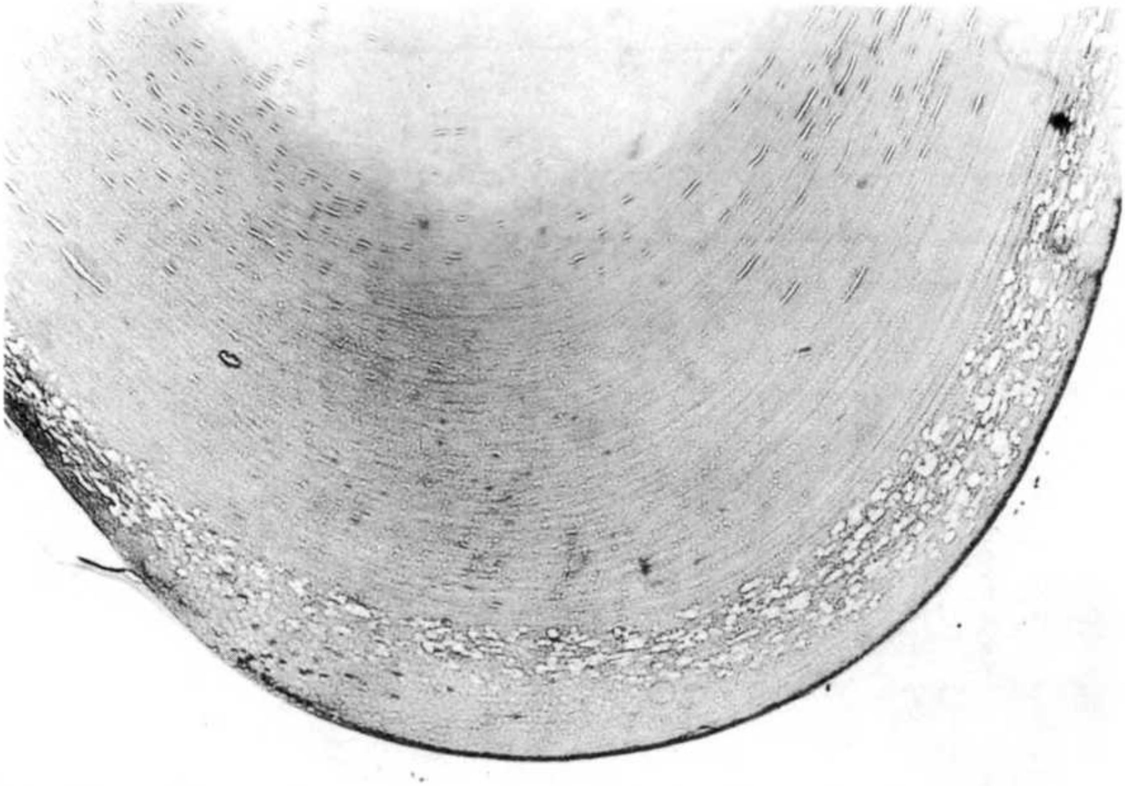

Fig. 3 *Lens with cataractous changes and bladder cell degeneration of cortex. (Haematoxylin and eosin, ×74).*

The retina displayed a Lange's fold and was well differentiated with a prominent nerve fibre layer. In the peripapillary area the retina was laterally displaced, and there was proliferation of glial tissue and extracellular oedematous spaces. The choroid appeared unremarkable. The optic nerve showed glial proliferation and extracellular oedema on the nerve head.

The following special stains were used to study the optic nerve: myelin, Bodian, alcian blue, and luxol fast blue. These stains demonstrated a segmental dropout of the axonal elements and myelin directly posterior to the lamina cribrosa. There were also areas of mucopolysaccharide within the nerve. The optic atrophy appeared segmental, with the more posterior nerve tissue appearing more normal. No inflammatory changes were identified.

DIAGNOSIS

(1) Cataractous changes (Fig. 3). (2) Optic disc oedema (Fig. 4). (3) Segmental optic atrophy with loss of axonal and myelin elements (Fig. 5).

Discussion

This report emphasises the ophthalmic features of the Majewski type of short rib polydactyly. Previous reports of these syndromes have been concerned primarily with the striking skeletal and visceral anomalies particularly as they relate to the differential diagnosis. While the ophthalmic features are not as striking as other aspects of the condition and not as prominent a feature as in other congenital syndromes such as 13 trisomy or Meckel syndrome, they nevertheless contribute to the pathological description of the syndrome. The present case represents a relatively mild form of the SRP syndrome as shown by the prolonged survival and the lack of visceral findings. It may well be that more severe cases would have a wider range of ocular abnormalities, and it is hoped that ocular histopathological study will be possible in future cases.

The association of neonatal dwarfism with polydactyly, narrow thorax, and other skeletal and visceral anomalies requires consideration of several

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diagnostic entities. The Majewski form of short rib polydactyly is distinguished by the usual presence of a cleft lip or palate, hypoplastic epiglottis, and lung and visceral abnormalities. A comparison of the present case with representative cases of the Majewski form is presented in Table 1 and may indicate a partial penetrance in our case.[10] Differential features of SRP type II are presented in Table 2 and include the presence of an abnormal pelvis, ragged metaphyses, gastrointestinal and genitourinary atresia, polycystic kidneys, and transposition of the great vessels.

Differential features of chondroectodermal dysplasia are also presented and include the absence of gastrointestinal and genitourinary changes, the absence of cleft palate or lip, the mild involvement of

Table 1 *Comparison of cases of SRP I*

	Present Case	*Majewski et al.*[5] *Case I*	*Spranger et al.*[7]
Birth weight	3250 g	2980 g	3500 g
Length	50 cm	44 cm	38 cm
Hydropic appearance	+	+	+
Narrow thorax	+	+	+
Polydactyly	+	+	+
Short tibia	+	+	+
Cleft lip/palate	+	+	+
Polycystic kidney	−	−	+
Genital anomaly	−	+	−
Cardiac anomaly	−	+	−
Immediate death	−	+	+

+ = Present. − = Absent.

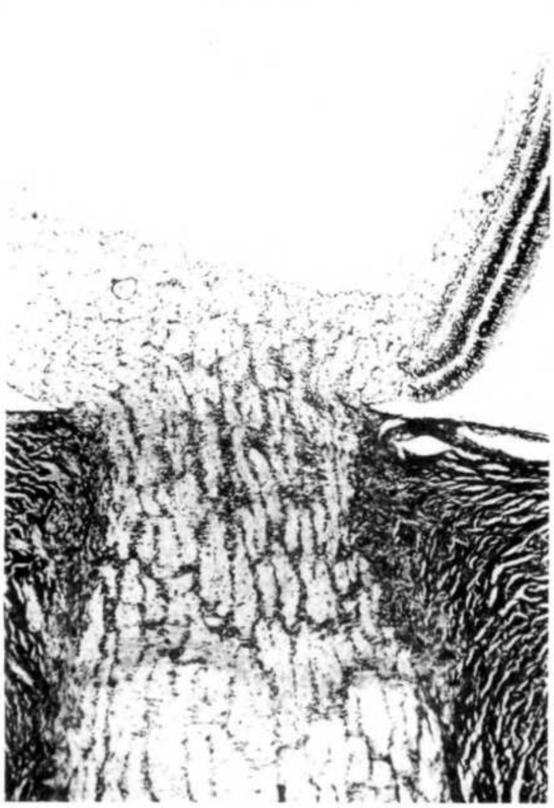

Fig. 4 *Optic nerve head oedema and glial proliferation. (Luxol fast blue, ×6·3).*

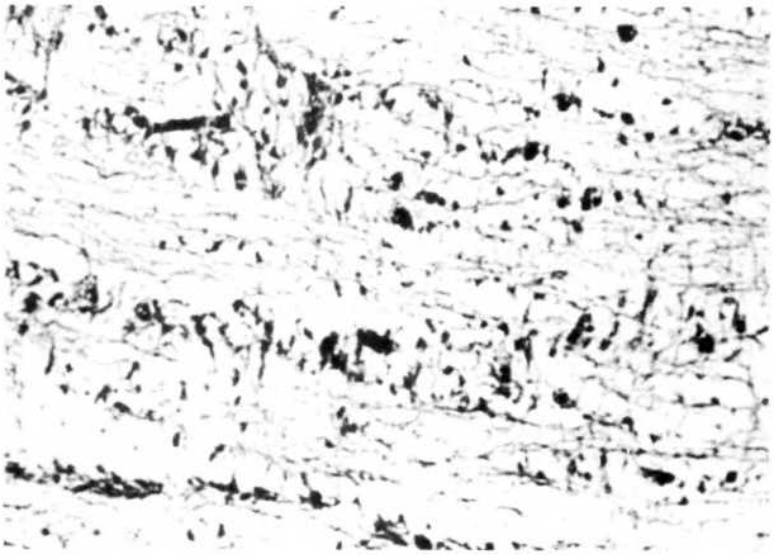

Fig. 5 *Optic nerve showing axonal dropout and myelin loss posterior to lamina cribrosa. (Bodian, ×40).*

Table 2 *Differential features of 3 congenital syndromes*

	SRP I (Majewski)	*SRP II (Saldino-Noonan)*	*CED Chondroectodermal dysplasia (Ellis-Van Creveld)*
GI and GU atresia	–	++	–
Pulmonary hypoplasia	++	++	++
Cardiac malformation	+	++	+
Epiglottic defect	++	+	–
Proximal skeletal changes	++	+	+
Tibial involvement	++	+	+
Deficient ossification	–	++	–
Metaphyseal dysplasia	–	++	–
Skull, vertebral, pelvic involvement	–	++	+
Nail dysplasia	–	–	++

+=Present. ++=Prominent. –=Absent. GI=gastrointestinal GU=genitourinary.

the proximal long bones, and the smooth metaphyseal margins (Table 2).

Polydactyly may be associated with other congenital syndromes with ophthalmic involvement. The Meckel syndrome is characterised by many severe abnormalities including posterior encephalocele, sloping forehead, microcephaly, cleft lip and palate, polycystic kidneys, and ambiguous genitalia.[17] A normal chromosome karyotype, polydactyly, and neonatal death are features seen in common with the Majewski SRP syndrome. Absence of the prominent skeletal features of the Majewski syndrome is an additional distinguishing feature. These systemic features are summarised in Table 3.

The ophthalmic features of the Meckel syndrome are both variable and pronounced and include microphthalmos, retinal dysplasia, rudimentary iris or aniridia, optic nerve hypoplasia, cryptophthalmos, sclerocornea, incomplete cleavage of the chamber angle, tunica vasculosa lentis, persistence of nuclei in lens fibres, and hypoplasia of retinal nerve fibre and ganglion cell layers.[18] Ophthalmic features are summarised in Table 4.

Polydactyly may be seen in the trisomy 13 syndrome. Cleft palate and visceral abnormalities may also be present but skeletal abnormalities are not prominent features. The ophthalmic findings are pronounced and include anophthalmia, microphthalmia, colobomata, cataracts, hypertelorism, and small orbits. Deafness, motor seizures, mental retardation, and neonatal death are additional features (Tables 3 and 4).[18 19]

The ophthalmic findings in short rib polydactyly are limited in comparison with those seen in the conditions noted above (Table 5). Early cataractous changes and optic nerve atrophy and oedema were found in our patient. The cause of this pathology is uncertain. Absence of intracranial space-occupying lesions or local ocular causes for the optic nerve changes raise the possibility of a toxic neuropathy, particularly in view of the 'anoxic and metabolic encephalopathy' observed on neuropathological examination. A further consideration would be the fact that the severe restrictive respiratory condition of

Table 3 *Systemic features of 4 congenital syndromes*

	Short rib polydactyly	*Meckel syndrome*	*13 Trisomy*	*Chondroectodermal dysplasia (Ellis-Van Creveld)*
Occipital encephalocele	–	+	–	–
Cleft lip/palate	+	+	+	–
Polydactyly	+	+	+	+
Perinatal mortality	+	+	+	+/–
Normal chromosomes	+	+	–	+
Autosomal recessive	+	+	–	+
Microcephaly	–	+	+	–
Genital anomaly	+	+	–	–
Polycystic kidney	+	+	+	–
Cardiac defects	+	+	+	+
Sloping forehead	–	+	+	–
Micrognathia	–	+	+	–
Haemangiomas	–	–	+	–
Hernias	–	–	+	–
Narrow thorax	+	–	–	+
Short extremities	+	–	–	+
Hypoplastic epiglottis	+	+	–	–
Absent olfactory bulbs	+	+	–	–

+=Usually present. –=usually absent.

Table 4 *Ophthalmological findings in 3 syndromes*

	Short rib polydactyly	*Meckel syndrome*	*13 Trisomy*
Microphthalmia	–	+	+
Iris anomaly	–	+	+
Cataract	+	+	+
Retinal dysplasia	–	+	+
Optic nerve oedema	+	–	–
Optic nerve atrophy	+	–	–
Intraocular cartilage	–	–	+
Colobomata	–	+	+
Persistent pupillary membrane	+	+	+

+ = Usually present. – = usually absent.

Table 5 *Summary of ocular findings in SRP*

Present case	1.	Cataract
	2.	Optic disc oedema
	3.	Optic nerve atrophy
	4.	Lange's fold
Piepkorn *et al.*[8]	1.	Ocular hypertelorism
	2.	Absent lashes and brows
Cherstvoy *et al.*[10]	1.	Persistent pupillary membrane

the patient for the 8 weeks prior to his death would most likely have caused a hypercapnia and hypoxia, which is a known cause of disc oedema and its sequelae in other clinical entities. The study of the ophthalmic findings in additional cases of the SRP syndromes may increase our understanding of the pathophysiology of this condition.

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Correspondence

Vitelliform degeneration and butterfly-shaped pigment alterations

SIR, I read with interest Gutman *et al.*'s article[1] on vitelliform macular dystrophy (VMD) in the right eye and butterfly-shaped epithelial dystrophy (BED) in the left eye of a 22-year-old female. They suggested that these were both expressions of one and the same disease. They referred to the concept of 'patterned' or 'pattern' dystrophies of the retinal pigment epithelium (RPE) by Hsieh *et al.*[2] and Marmor and Byers,[3] in which publications reticular pigment alterations, butterfly-shaped and granular pigmentations occurred in 2 families on a presumed autosomal dominantly inherited manner. These last 2 publications did not mention the simultaneous occurrence of VMD and BED in one family, or even any similarity, as is erroneously stated by the authors.

Both Best's VMD and Deutman's BED are autosomal dominantly inherited dystrophies of the RPE and both may show severely depressed EOG ratios. Adult onset vitelliform lesions without a diminished EOG ratio and without any detectable heredity have been described only recently.[4,5] They are considered separate entities, different from Best's vitelliform degeneration. Deutman's butterfly-shaped foveal dystrophy is certainly another well-circumscribed nosological entity, which can be mimicked by several totally unrelated diseases: Stargardt's macular degeneration, acquired drusen of Bruch's membrane, rheumatic foveal degeneration,[6] and myotonic dystrophy.[7] We had already demonstrated in a patient with an adult-onset vitelliform macular lesion in the same eye a butterfly-shaped degeneration of the fovea,[6] as Deutman mentioned before us.[8]

I consider any pattern or patterned degeneration of the RPE as a totally aspecific response of the RPE to very different pathogenic stimuli. We could also demonstrate reticular pigment alterations of the posterior pole of the eye in a patient with choroidal folds, and in another with multiple RPE detachments.[6] A pattern(ed) dystrophy (which by its name implicates a hereditary disease) of the RPE does not exist, but there is certainly a pattern(ed) syndrome of the RPE, initiated by several different stimuli. So it is possible to find butterfly-shaped degenerative lesions of the RPE in patients with vitelliform disease of the RPE, even in these vitelliform lesions themselves.

There is no necessity to postulate a continuum or a common denominator for Best's VMD and Deutman's BED. Butterfly-shaped alterations can occur in a number of totally different RPE diseases, and possibly the same holds true for vitelliform lesions. There is no need either for the acceptance of the concept of pattern(ed) dystrophies of the RPE as a separate nosological entity. The existence of such a disease is the more unlikely because of the lumping together of autosomal recessive diseases (reticular and macroreticular RPE dystrophy),[9-11] as well as autosomal dominant diseases of the RPE (Deutman's BED and fundus pulverulentus). However, the presumed occurrence of autosomal dominant reticular and macroreticular degenerations of the RPE[12,13] adds to the confusion in designing a classification of the RPE diseases.

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Obituary

Jean M. Dollar, MS, FRCS, DOMS

Jean Dollar died on 20 April 1982 peacefully at home. She was born in London at the turn of the century. Her father, uncle, and grandfather were veterinary surgeons practising in Bond Street. After schooling in London she attended the London School of Medicine for Women and in 1926 graduated. She obtained the diploma in ophthalmic medicine and surgery in 1929, proceeding to her mastership in 1935 and final diploma of the Royal College of Surgeons in 1936. This same year she was appointed to the consultant staff of the Royal Eye Hospital, London. Her other consultant appointments included St Olave's, Elizabeth Garrett Anderson, and Royal Free Hospitals. In 1945 she was elected Hunterian professor at the Royal College of Surgeons of England.

Her main commitment throughout her working life was to the Royal Eye Hospital, where during the war of 1939–45 she was one of the few members of staff not on active service. In the initial postwar period the hospital was amalgamated with King's College Hospital. This link was severed in the mid 1950s, and as chairman of the Medical Committee she skilfully steered the hospital through an inevitably disruptive period. In succeeding years she was a long-standing member of the Group Management Committee.

She was a deft and gentle surgeon and in the early 1950s, together with a colleague, devised a technique of exenteration of the orbit and postoperative fitting of a prosthesis, enabling young patients with sarcoma of the orbit to have a more bearable period of life which was left to them. Her calm, reassuring approach endeared her to her patients, and her colleagues found her to be a strong member of their team, with a refreshing humour. Postgraduate and undergraduate students benefited from her teaching, which she enjoyed, latterly imparting great wisdom gained from her experience and often punctuated by poignant anecdotes. She gave stalwart support to nursing matters, and her interest in her patients extended beyond the hospital. She possessed and developed a unique association with medical social workers on their behalf.

Although not a physically energetic person, particularly in later years, she enjoyed walking on holidays, visiting places of archaeological or wild fauna interest. A reluctant housekeeper and gardener, her main leisure enjoyment was reading, so that, despite her natural shyness, she was an interesting and entertaining conversationalist. She retired from practice 17 years ago, and her death is a sad loss.

DOREEN A. BIRKS

Book reviews

Adler's Physiology of the Eye: Clinical Application. 7th edn. Ed. ROBERT A. MOSES. Pp. 747. C. V. Mosby: London. 1981.

This book lives up to the high standard of production shown in the previous (1975) edition, and, as before, it is designed to emphasise the clinical aspects of its subject matter. As with any book having a multiplicity of authors there is both overlapping and omission, but in general the editor and his team are to be complimented on a most useful textbook.

Most of the sections have been updated and extended, but it is rather surprising to find that the discussion of retinal neurotransmitters in the section on retina and optic nerve is practically the same as in the 1975 edition and that there is no mention of the technique of specular microscopy in the section dealing with the cornea. The section previously headed 'Iris and Pupil' is now simply 'Pupil,' and, while some material has been deleted, the discussion of iris pharmacology has been updated. The section on visual acuity has been rewritten, and, by contrast with the 6th edition, very little is said about the use of gratings. One would also have liked to see a little more about the role of timolol as an ocular hypotensive drug and some discussion of recent work on lens proteins.

These are, however, minor blemishes. On the positive side the new 'Adler' has a fresh lease of life in an edition only some 40 pages longer than its predecessor and containing as a new feature a 'Biological Index' which, apart from its intrinsic value to the reader, serves to indicate the importance of comparative studies in this field.

D. F. COLE

Guidelines for Programmes for the Prevention of Blindness. World Health Organization. Pp. 47. No price given. WHO: Geneva. 1979.

This is a work of reference which can be adapted as required for the planning of national or regional programmes for the prevention of blindness.

It was prepared at a meeting held in Asilomar, California, USA, in October 1978 and jointly sponsored by the WHO centre for reference and research on trachoma and other chlamydial infections, the FI Proctor Foundation, San Francisco, the International Eye Foundation, and the World Health Organisation.

There were 40 participants at the meeting representing the following countries—USA, Britain, Australia, Switzerland, China, Nigeria, Peru, Egypt, Guatemala, Upper Volta, Sri Lanka, Barbados, Kenya, and Indonesia.

It was agreed that most of the blindness that affects some 30 or 40 million people in the world mainly occurs in the less developed areas where malnutrition and infections are common, and it is potentially avoidable. The goal of the WHO programme for the prevention of blindness is to eliminate the burden of avoidable blindness, for which there are many simple and effective preventive measures that can be applied.

It was decided that the 4 principles for action in a national programme to eliminate avoidable blindness and visual impairment are: (1) the identification of communities with a high prevalence of avoidable blindness and determination of its cause; (2) the provision of early treatment to the worst affected communities by using preventive and therapeutic measures, and when there is an accumulation of patients in need of surgery (e.g., for cataract or distorted eyelids) surgical treatment should be carried out if a mobile surgical team is available; (3) the establishment of therapeutic and preventive measures for the promotion of eye health; (4) the improvement of ophthalmic services so as to provide an adequate referral system and a centre where supervision and training of personnel can be carried out.

It is emphasised that an effective blindness-prevention programme cannot be accomplished by the medical profession alone. Intervention must be based on the presence of cultural and social factors, general education, food production, nutrition, water supply, and transport, and it needs support from public and private sectors. An assessment of 'ocular status' (i.e., an investigation of the magnitude and causes of blindness within the region or country) is essential in order to plan an effective programme. Committees should, if possible, be set up consisting of government representatives, ophthalmologists, and specialists in public health and leaders in industry and in the media.

Auxiliary workers who have been adequately trained should be employed for most routine procedures including vision screening, but full examination of the eyes should always be done by a person specially trained in ophthalmology. House-to-house examination by a survey team in conjunction with a central examination clinic is valuable, and members of the team should be prepared to treat all eye conditions which are amenable to topical therapy. An assessment of the economic resources of the country should be made and should include—statistics of births and of diseases, environment, and sanitation, facts in regard to general health and nutrition, education, and teaching, and transport and communication, and standard of general management and leadership. Local personnel who are a useful resource for help in giving instruction in eye health include teachers, social workers, local religious leaders and community workers, and of course ophthalmic nurses and assistants, optometrists, opticians, and orthoptists.

The 3 stages of eye care which should be available are described as follows. (1) *Primary eye care* which should be in accordance with the principles of primary health care and must include therapeutic and preventive activities and the promotion of eye health. It should provide treatment for conditions such as conjunctivitis, especially trachoma, superficial foreign bodies, minor trauma, and xerophthalmia. (2) *Secondary eye care,* which should be an integral part of general secondary medical care, should provide treatment for ocular trauma, cataract, corneal ulceration, intraocular infection, entropion, pterygium, and possibly glaucoma. (3) *Tertiary eye care units* are usually established in national or regional capitals and are preferably associated with a hospital which has a medical school. They should provide more sophisticated eye care such as surgery for the correction of detached retina, corneal grafting, and other more complex forms of treatment including treatment of eye conditions due to medical and neurological diseases. Close co-operation with peripheral units should be maintained so that the staff of tertiary centres should be available to participate in the work of primary and secondary units.

The methods recommended for control of trachoma, nutritional blindness, onchocerciasis, and cataract are summarised, and also the use of mobile services.

The training of primary health workers should include eye care as part of their duties. The training of ophthalmic assistants should be undertaken by ophthalmologists. They should be taught minor surgical procedures such as operation for chalazion and removal of corneal foreign bodies. Qualified nurses, because of their training, are particularly well suited for this job.

There are a number of intergovernmental and nongovernmental organisations to which national governments may turn for support in order to establish programmes for the prevention of blindness. The World Health Organisation has taken the lead in international action to assist national programmes. Its financial resources are limited but it provides liaison with a variety of governmental and nongovernmental agencies and helps the mobilisation of efforts and funds both within and outside its own organisational structure.

International nongovernmental organisations which are active in this field and are in official relations with WHO are the International Agency for the Prevention of Blindness, the International Federation of Ophthalmological Societies, the International Organisation against Trachoma, and the World Council for the Welfare of the Blind. Other agencies with broad international programmes or interests include the Christoffel Blinden Mission, Helen Keller International Inc., the International Eye Foundation, and the Royal Commonwealth Society for the Blind and many others.

The publication has 4 Annexes. The first is a useful list of definitions and explanations of some of the terms used, and the second gives the coding of eye conditions in accordance with the 9th (1975) Revision of the International Classification of Eye Diseases. The third is a selected recent list of pertinent WHO publications, and the fourth gives a list of the names of participants at the Asilomar meeting.

T. KEITH LYLE

Notes

Vitreoretinal symposium

The Lake Tahoe Vitreoretinal Symposium, sponsored by the Retinal Faculty, University of California Davis School of Medicine, will be held at Granlibakken Ski Resort, Tahoe City, California 95730, USA, on 6-10 February 1983. Details from Donald May, MD, 2315 Stockton Boulevard, Sacramento, California 95817, USA.

Microsurgical teaching workshop

A microsurgical teaching workshop will be held in Hong Kong on 18 and 19 March 1983 in conjunction with the 9th Congress of the Asia Pacific Academy of Ophthalmology. This meeting is jointly organised by the Royal Australian college of Ophthalmologists and the Asia Pacific Academy of Ophthalmology. Details from Dr Arthur S. M. Lim, Chairman of the Organising Committee, Unit 0609, Mount Elizabeth Medical Centre, Mount Elizabeth Road, Singapore 0922.

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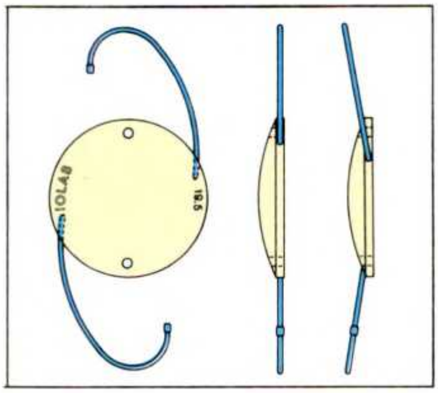

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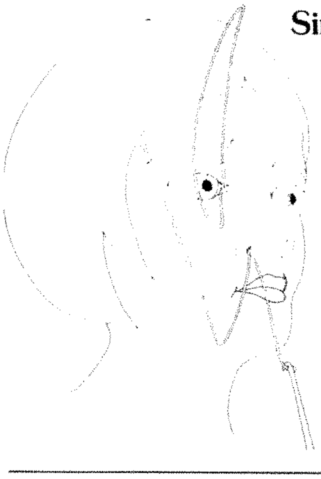

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OPHTHALMIC PUBLISHING COMPANY
Suite 1415, 435 North Michigan Avenue, Chicago, Illinois 60611, U.S.A.

Published by British Medical Association, Tavistock Square, London WC1H 9JR.
Typesetting by Bedford Typesetters Ltd., Bedford, England. Printed by Paramount Printing Co. Ltd., Hong Kong

British Journal of Ophthalmology November 1982 Vol. 66 No. 11

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British Medical Association Tavistock Square London WC1H 9JR